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The Hazards of Radiation[1]

Edward Teller, Ph.D.

Los Angeles

Ladies and Gentlemen, it is a very great honor for me to be with you today and it is a particularly great honor to be asked to give this lecture in memory of our good and very great friend, Dr. Ernest O. Lawrence. In his life he has done a great many remarkable things. He was a builder, and the influence of his work reached from the investigation of the nucleus to national defense and from there again, very significantly, to the health of all of us. When he developed the instrument for accelerating particles, a development in which he stands above everybody, he had in mind all along to use the new nuclear tools for the purposes of medicine. In the Radiation Laboratory isotopes have been produced at an early time and there were many years when the Radiation Laboratory was *the* source of isotopes for the whole world. Because of his initiative and enthusiasm we in this Country have a very considerable headstart in nuclear medicine.

This is the headstart which we have used well. I shall mention two very obvious uses. One concerns our fight against the greatest remaining danger to human health: cancer. At least in certain stages some cancer cells are more sensitive to radiation than the rest of the body. Thus radioisotopes can be of help in the treatment of cancer. The other point is even more important. With the help of isotopes one can follow the particular way in which any element goes through the complicated maze of biological activity, and in this way we can have a detailed and instructive insight into biochemical processes.

In addition to these great fields that I have mentioned, Ernest had a deep interest in one thing. He saw that the scientific results concerning radiation have been misunderstood, and he tried to set the record straight. It is this topic which I want to discuss with you today.

We have all heard about radiation hazards. We all know that people are greatly worried about these hazards. This danger has been exaggerated. There is a story which many of you may have heard, but I will repeat it because it illustrates Ernest's interest in this particular point.

[1]First Annual (Pioneers in Nuclear Medicine); Lecture—presented at the 7th Annual Meeting, Society of Nuclear Medicine, Estes Park, Colorado, June 25, 1960.

When the 37-inch cyclotron started to function in 1935 and when neutrons began to come out of this instrument, one of the very obvious questions was whether the effects of the neutrons will be similar to the effects of x-rays, gamma rays, electrons, alpha particles and other radiation. Because this question arose, Dr. John Lawrence and Dr. Paul Aebersold rigged up a little apparatus with a rat inside, which had to be jammed into a very narrow space in the cyclotron. The rat confined in this narrow space was supplied with air which came through a little tube. The cyclotron was turned on. It ran for two minutes; Ernest said we better stop, look and see. He stopped and looked and the poor rat was dead. This caused an enormous consternation because the rat did not get a really big dose. It appeared that the neutrons were much more dangerous than any other radiation. Well, it took a little time to find out the real story: the tube which supplied the blasts of air to the rat was closed during the test and the rat suffocated.

This, ladies and gentlemen, was the first of many alarms about radiation, and like the rest of the alarms, it had little foundation. Unlike some of the other alarms, however, it had an advantage. It made all the people in the Radiation Laboratory very conscious of the possible danger of radiation, and partly because of care and I should say partly because of good luck, there has been a really excellent record of radiation safety in the Radiation Laboratory.

Starting from these early observations an important conclusion developed: Nuclear radiation and radiation damage is a simple thing. The effect of radiation is to tear molecules apart. There is nothing particularly specific in this. Some types of radiation are two or three times more effective than some other radiation, but by and large any radiation acts in a similar way as long as it gets into touch with tissues. The main question is, how much energy is delivered and to which tissues. Of course, the overall action may appear quite different. You may have penetrating radiation which traverses the whole body, or soft radiation which stops in the skin. There can be radiation from isotopes which are deposited in certain organs, and only these organs will be irradiated. But as long as some tissue is irradiated, the effect of the radiation is reasonably accurately estimated, if not really measured, by the amount of radiation energy delivered to that tissue.

This is in exceedingly sharp contrast with the effects of chemical agents which have a key and lock property. A molecule in which you have made a little substitution can change from a food into a poison. And to predict on the basis of chemical evidence, the biological effects is beyond our present knowledge and may remain so for some time. Therefore, to begin with, radiation is a much simpler agent. But I hope that you will not draw the conclusion from this that therefore its effects upon us are simple. While radiation is simple, we unfortunately are complicated. You do something to us, and God knows how we are going to react.

The topic which I first want to discuss and which I want to keep in the forefront for quite some time is the danger from the worldwide distribution of radiation—the worldwide fallout from nuclear tests. And this is the very point that some of us, very much including Ernest, have discussed frequently and carefully.

The question of fallout has really nothing to do with nuclear testing. We have learned that we can perform the needed nuclear explosions either underground or in outer space, and we can get in this way practically all the information which we need. And this way of performing tests is in my mind easier, more rational, precisely because it does not contaminate the atmosphere.

Radiation has the same property as everything in the world. It is very dangerous if you get too much of it. In the neighborhood of a nuclear explosion you do get too much of it. And therefore the immediate neighborhood of nuclear explosions must be watched carefully. It is therefore very much better if you want to make nuclear explosions to put them somewhere where they cannot get in touch with anything alive. That means put them very deeply underground; put them outside the earth's atmosphere, and then you can be safe. The question whether or not to continue nuclear tests is a political question and is quite independent of the discussion which we are going to have today here.

The scare about worldwide fallout is something about which we must have clear understanding, because it interacts with many problems with very specific medical problems. As you know, there has been quite a bit of controversy about nuclear fallout. Some people believe—maybe some of you believe—that this controversy has been in part caused by the circumstance that nuclear explosions, nuclear testing and the fallout that comes from nuclear testing has been secret and therefore the general public, even physicians like you, did not have an opportunity to be fully informed. This statement is only partially right. In fact, in the main it is just plain wrong. Information about distribution of nuclear contamination has been kept secret prior to 1953. In the year immediately preceding 1955 all of this information was available to the public. Suspicion did continue that some facts are held back. This is not true. The record is public and the record is complete. Then after the record was complete, radioactivity was dragged into the political arena in the election of 1956.

Let me try to tell you how some propagandists who try to scare the people summarize their argument. Their summary is effective, it is simple, and it has the appearance of fact. The summary goes like this. We know that the exceedingly small doses of radiation which the worldwide distribution of fallout will give to the individual has a very small chance to harm an individual, one chance in 100,000, or perhaps one chance in a million. But there are very many people in the world, and if there is one chance in a million then 3,000 people will be hurt, and if there is one chance in 100,000, 30,000 people will be hurt. We should not hurt thousands of people.

This argument, while it sounds simple and plausible, is wrong. Fallout has so small an effect that nobody ever has observed it. And nobody knows either from direct observation, or from statistics, or from any valid theory whether the claimed damages in fact exist or do not exist. I want to talk about that a lot more, because talking about the effects of various doses of radiation leads us immediately into an interesting field of research which should be important for all of us. The plain fact is that we do not know what are the effects of small doses of radiation.

At this point the opponents of testing argue: "All right, we do not know whether this radiation is dangerous or not. Therefore, wouldn't you think that as long as we do not know whether it is dangerous or not we should abstain from spreading such radiation around?" This again sounds like an emminently reasonable argument, and I would say there is a little bit of truth in it, but only a little bit. There is considerable evidence that the real effects are very considerably smaller than the effects which I have mentioned. I believe that exceedingly few people have been actually harmed by fallout, possibly the opposite may have been the case. Radiation might have beneficial effects.

Before we continue this argument I want to put before you some simple facts. *Fact Number One* I have already put before you: essentially all radiation acts in a similar way. How it will act in very small doses we do not know. But we know that small doses of neutrons, small doses of x-rays, of gamma rays, of beta rays, of alpha rays, and of cosmic radiation will all act very similarly. We know this from physical evidence; we know it from chemical evidence; we know it from a concurrence of a great deal of biological information.

Fact Number Two is this: For more than one hundred million years, ever since fish took the courage to emerge from the ocean, all of our living ancestors have been exposed to cosmic rays. And even those of our ancestors who were sheltered by many feet of sea water drank radioactive potassium and other materials; even those were not exempt from radioactivity. The natural background of radiation to which we and our ancestors have been exposed is approximately fifty times as great as the radiation which we get from all the fallout about which you have heard so much. In addition, we are exposing ourselves for good reason to medical x-rays.

Let us consider first only diagnostic x-rays and not the much discussed therapeutic doses. These diagnostic x-rays which an average healthy individual gets in his life amount to about as much as the natural background. Therefore the amount of radiation that the average individual is getting is one hundred times as great as the fallout which we are getting. More than that, natural radiation changes from place to place a great deal. You are courageous people for having come up here to Colorado. Do you realize that you are 7,000 feet closer to the sky, that there is less air between you and the heavens, and the cosmic radiation, which is much stronger than fallout, is beating on you with a much greater intensity than any you could expect from fallout even where fallout is concentrated. I do not know how many of you are as foolhardy as I am to carry a radioactive wrist watch which is hardly visible to your eyes if you try to look at it at night, but nevertheless sends a Geiger counter into frantic activity. The natural background about which we usually do not hear, about which we usually do not worry is greater and its changes from one place to another are greater than anything you can expect from fallout. This natural background will be different if you are higher up. It will be different and greater if you live in a brick house. It will be different if you change your diet. It will be different if you live in a part of the Country where there is a little bit more thorium or uranium in the ground. All the prophets of doom are silent about these dangers which are much greater than the dangers about which they preach.

Could it conceivably be that, knowingly or not, these people are worrying about something else than radiation when they talk about fallout. I understand, gentlemen, that we here are modest people, interested in nuclear medicine and not in psychiatry or politics. Therefore, this last question I will have to leave unanswered.

I would like to make an appeal to you. A few years ago there has been introduced a concept which seems useful—the maximum permissible exposure of a person. I say that this concept seems useful. I also say that this concept is most disturbing, misleading, dangerous, and that you should get rid of it. We do not know what the effects of small irradiations are. Therefore we cannot tell what is the maximum permissible exposure. And since most of the people who make such decisions are conservative, they set the maximum permissible exposure as low as possible so as to be really safe. Probably ten or one hundred times the permissible dose will not cause damage either. Yet, figures are published and then somebody finds out: "I've had twenty percent of the maximum permissible exposure. I have gone twenty percent towards some kind of a disaster which I do not understand, but which quite possibly is as bad as getting cancer." The alarm that has been spread by this word, "maximum permissible exposure", has been tremendous. And then the experts get frightened and lower the maximum permissible exposure by a factor 2, and then everybody says: "When will they lower it again? Perhaps I already have the maximum permissible exposure."

Recently better words have been introduced. Instead of "maximum permissible exposure" we should use the "Radiation Exposure Guide," a guide which will be different when you expose the whole population, different and higher for professions, different, still higher in emergency situations where some chances have to be taken. It is also complicated, and I would advocate that we don't talk too much in public about this guide.

I would advocate that we should talk in public about one thing only. We should agree on the average background exposure. Assume the average background exposure is one-tenth of an "r" per year. Let us agree on a firm figure and then let us tell people. The maximum permissible dose is a figment of man's imagination. The average background comes from God, and furthermore since everybody is exposed to it, is a much more reasonable and democratic unit. It is also much more reassuring.

The public has been scared into an unreasonable behavior. Those of us who have the information must talk not only to their own patients but to the public and must counteract the unreasonable and unscientific fear mongers.

I would now like to talk to you about some more interesting questions concerning fallout. What is probably the real danger? It has been estimated by many that due to fallout the lives of some 20,000 or 50,000 people might be shortened. All of this has been based on a very simple hypothesis. And because it is simple, therefore it is plausible. And because it is plausible it is widely used. And because it is widely used it is widely believed. Yet, the connection between this hypothesis and truth is exceedingly tenuous.

The hypothesis is that if one thousand "r" units do a certain damage or do damage with a certain probability, the one "r" unit will cause the same damage with one-thousandth that probability. This statement is based on the single-hit theory, that is, the idea that if one molecule is disrupted, the disruption of this one molecule is irremediable and will produce an ultimate consequence with a fixed probability.

Examples of the opposite abound. We know that something like five hundred "r" units delivered in one dose will kill half the people if they are healthy, and more if they are not. Yet, we know that we can in fractionated amounts deliver one thousand or two thousand "r" units without any danger of short-time injury, although some clear-cut danger of long-range development of some disastrous diseases exist. Proportionality between dosage and effect is certainly not demonstrated. In fact, there is no good statistical evidence of any damage to the individual, unless that individual got approximately one hundred "r" units. At the same time, if he gets five hundred "r" units in one dose, he has a fifty percent chance of dying. Therefore the full range in which proportionality between cause and effect can be explored is only a range of five-fold change in radiation. In this range the experiments are complicated and conflicting; some of the evidence clearly contradicts proportionality; other evidence seems to show proportionality but in an unclear manner. The evidence is derived from laboratory experiments, from irradiated populations in Hiroshima and Nagasaki, and it comes from therapeutic applications or radiation. The upshot of these results is that no clear-cut evidence is obtained for proportionality in any pathogenic effect.

There have been animal experiments with low-level irradiation. Even this low-level radiation is one hundred times as great as the fallout, and there are essentially no experiments with as low a level as the fallout. The low-level irradiations have been carried out by Dr. Lorenz in the National Institute of Health, Dr. Carlson at Washington State. There are some indications that when you expose mice and rats to these low-level radiations, these animals live ten percent longer. Many people say the evidence is incomplete, and I must add on my own—they look incomplete to me. I don't know whether the evidence is conclusive. The simple fact is that when you get to very low levels of irradiation you do not know whether the effect is proportional to the first power of the radiation, whether it is proportional to a high power of radiation, whether it has a threshold so that below that threshold there is no damage or whether below a certain threshold there even are beneficial effects.

Radioactive waters used to be advertised as beneficial. This claim was unscientific. But the opposite claim that all radioactivity is harmful is not much more scientific either. We simply do not know.

I believe that some effects are proportional but probably only a very few, because most processes in our bodies are likely to be more complicated and are not due to one single event. The very idea that cancer could be caused by one single event flies in the fact of general experience like precancerous stages, which shows that cancer develops in several stages rather than being due to one single cause.

Now I would like to mention to you another field about which we have been fully as much disturbed—the genetic effects of radiation. In the genetic effects the situation is different. Very detailed studies have shown that irradiation of the spermatozoa of fruit flies give rise to mutations strictly proportional to the dose, and therefore proportionality has been demonstrated in a wide range between twenty-five "r" units and four thousand "r" units. I think this is good, solid, scientific work. But the results are different for the spermatogonia and for the Oocytes. If you have a bare cell nucleus which is stripped down to the genetic apparatus and contains nothing else, like the spermatozoa, then indeed the effects are simply proportional to radiation, and the single-hit theory seems to be supported. If you deal with spermatogonia, the situation is more complicated. Then you deal with a cell nucleus and a cell body and the effects of radiation depend on the dose rate. The effect becomes smaller if instead of a single dose you fractionate your dose. Repair mechanisms seem to become possible, and only strong irradiation in one dose is really damaging. The same seems to hold for the female cells, for the ovum. In worldwide fallout the dose rate is small. Spermatogonia and ooza may not be damaged at all.

We have heard that fallout produces a terrific genetic burden. To begin with, radiation from fallout is only one percent of the radiation which we are getting anyway. Secondly, I do not think that all mutations are harmful. All mutations of course are abnormal because only what is not mutated is what we call normal; and as every reasonable group of individuals we believe that we are the peak of creation. But really to believe this, not emotionally, but intellectually, would seem to deny the simple fact of evolution. You must allow that something that is new might be better.

Mutations are increased by fallout, but probably by less than one precent. Many mutations in us are probably due to the spermatogonia and oozoa. In these fallout probably produces practically no effect. Furthermore, some very excellent Swedish research men have pointed out that mutations are caused because we are foolish enough to wear trousers. This causes a temperature change in one of our organs; this will lead to a mutation rate surpassing the effects of fallout more than hundredfold. The Swedish geneticists therefore recommended that the prophets of genetic doom should wear kilts.

There is, ladies and gentlemen, one little point which I would like to make in all seriousness. There can be very little doubt that the modern medical art can keep people alive who otherwise would die. This increases the number of surviving mutations. For instance, a person who has diabetes can live longer and have children. This probably increases the genetic burden much more than fallout. In a humanitarian sense it is obviously correct to save lives. Furthermore, I do not think that this is necessarily a disadvantage from the point of view of the evolution of the race. Why do we have mutations? Due to mutations we can adapt ourselves. Can you think of an age which changes more rapidly than ours? Can you think of an age where adaptation is more necessary than it is in ours? By allowing more mutants to survive we allow more adaptation. Perhaps those among us who have diabetes and who can now be kept alive have a linked

property of being tempermentally more suited to live peacefully with their neighbors. Perhaps they are on the average more intelligent. Nobody knows. I think that the expression, "genetic burden", is ill chosen.

Fallout is not dangerous. But the fallout scare is. Many people know that a medical x-ray gives you one hundred times as great a dose as fallout will give you in your whole life-time. How many people have been scared away from x-rays? How many people have gone with their ailments unrecognized and untreated, only because there has been this needless and exaggerated fallout scare? I don't know. I don't know whether anybody has been killed by fallout, but I am sure that many have been killed by the fallout scare.

There are many cases in which people were frightened away from the much more massive therapeutical doses. A year ago my sister had trouble with her thyroid. The tissue had to be removed either by an operation or by the iodine treatment. You all know that the operation has some small hazards. You know also that radioactive iodine treatment is simple, painless and safe. My mother, who is a great worrier, almost prevented the iodine treatment, and it took all my eloquence to put it through. I wonder how many are the cases in which people have abstained from needed radiation treatment because of the fallout scare. There must be many, many such cases.

It is not unusual that in a serious case of cancer, a surgeon will undertake an operation, which is dangerous. He will tell the patient that there is a chance that he will die during or immediately after the operation, and in such a serious operation it is not at all unusual to accept a hazard, of let us say to 20 percent. As far as I know, in the case of radiation treatment no hazard is ever accepted. If there is a hazard of death we abstain from the treatment. I do not see any logical or sensible reason for this distinction. Either the procedure of the surgeon is too radical or else our procedure with radiation is too conservative. Perhaps our conservatism at present can be defended on the basis that in many cases we may not yet know enough. But in principle there must not be any difference between the two. Radiation damage is considered today as something unknown, new, dreadful, something that has to be avoided under all circumstances. I think this is unrealistic, and I think that this lack of realism has cost many people their lives.

This lack of realism can be removed only by very thorough public education. The problem of explaining radiation hazards is essentially the same whether you explain the practically nonexistent hazard or fallout, whether you explain the hardly more existent hazard of diagnostic x-rays, or whether you are talking about therapeutic x-rays or irradiations which are necessarily hazardous. In all three cases public education is essential, and public education can be undertaken by no one as effectively as by you.

I know that Ernest Lawrence would not want me to conclude my talk without emphasizing some positive aspects of nuclear medicine. We are finding out more about the effects of radiation. This will result in more faith in the use of radiation. It will result and it should result in a wider application of radiation for therapeutic purposes, as a diagnostic tool, and particularly as a research tool.

There are two great killers left. One, the degenerative circulatory diseases; the other cancer. In both of these cases the research that is needed in order to bring help is research which can be done much better with the help of radioactive isotopes than in any other way. With the help of radioactive isotopes you might be able to follow the slow growth, the slow deposition of unwanted substances on the walls of an artery or the slow changes in any other organ. With the help of radioactive isotopes you can find what chemicals will go to this or that cell, to a healthy cell or to a cancerous cell. In this way we might be able to get closer to a meaningful chemotherapy of cancer, whether this be chemotherapy using chemicals that we synthesize or whether it be chemicals of a more complicated kind, which are called antigens. It is even possible that the miracle of the cure of thyroid cancer can be repeated, that we can incorporate radioactive isotopes into some molecules which will seek out the cancer cells even after they have been distributed all over the body, and in this way get rid of a cancerous condition in a stage in which no other method is likely to help.

We have so far used in our radioactive research a relatively small number of radioactive isotopes, namely, those which live long enough so that they can be made and then distributed and then used at leisure. There are many more radioactive isotopes of a short life. Using these you could open up the whole periodic system for the purpose of research and for the purpose of therapeutic irradiation. You might be able to inject a radioactive isotope in a very specific location and before the isotope had much of a chance to migrate away from the location it would have decayed. Of course, if you want to use these isotopes you have to have the source of these isotopes readily available. Fortunately, the sources of isotopes have become very much cheaper. For instance, the Triga reactor which you have seen yesterday is a good example of a relatively small, inexpensive and safe nuclear reactor. I hope that nuclear reactors of various kind might appear in all medical research centers, perhaps in all hospitals. You can inject the activated substance seconds after it has left the reactor and in this way you might be able to use for your research, diagnostic or therapeutic work isotopes which have as short a lifetime as a minute or two. We need these isotopes to unravel biochemistry and to get even closer to this mysterious complication which we call life.

Ernest had a very unusual ability of taking pleasure in progress, quite independently of whether he or someone else made that progress. I hope that this spirit will prevail among us. Only by taking pleasure in our mutual achievements, only by going ahead with confidence and courage, will it be possible to master the enormously complicated field of biochemistry, the science of life.

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A Focusing Collimator for Research in Scanning[1]

J. E. Francis, Jr., C. C. Harris and P. R. Bell

Oak Ridge, Tennessee

In recent years, people who use gamma-ray scanning as a clinical procedure or as a research technique have become more critical of their equipment. Instruments that will grossly outline a gland or show the mere existence of a tumor are no longer considered adequate. There is a growing desire to see more detail faster, using less dose, under more adverse conditions. This paper will describe the latest directional gamma-ray detector developed at Oak Ridge National Laboratory. This focusing collimator-shield combination was developed in an effort to improve scanning as a technique for research and clinical medicine.

Figure 1 shows a cross-section view of the new directional detector. Gamma rays are detected by a 3-inch diameter by 2-inch thick NaI(Tl) crystal integrally mounted on a 3-inch multiplying phototube. The crystal is housed in a massive tungsten-alloy shield, two inches thick at the sides and three inches thick at the front. The "focusing" element is a conical gold insert with 37 tapered hexagonal holes focused on a point three inches from its front face.

Because of the use of tungsten and gold, this assembly is more expensive than present-day lead collimating shields. It is believed that the increased expense may be justified by the unremarkably improved performance provided by the use of tungsten and gold instead of lead.

Early focusing collimators (1,2) made possible improved thyroid scans with lower doses than formerly obtained. The scans thus obtained, however, contained evidence that the shielding—afforded by the sides of the assembly and the walls between the holes of the focusing element—was inadequate. The evidence consisted mainly of the fact that the counting rates obtained with the detector aimed at a patient's pillow were no lower than those obtained with the detector aimed at the side of the patient's neck. When the detector is aimed at a point other than the thyroid gland, the gland becomes a source of "background" or undesired signal. This evidence was disregarded by many people.

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[1]Oak Ridge National Laboratory, operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

When these same detectors were used in attempts to localize intracranial lesions, the inadequacy of the shielding was clearly demonstrated. At present, there have been reported no radioactively tagged pharmaceuticals that concentrate specifically—to any great degree—in brain lesions. In brain scanning, the greatest part, by far, of an administered tracer will be found elsewhere in the body than in the head. The upper part of the body may contain as much as a hundred times the activity in the cranium. Therefore, a detector aimed at the head must detect a weak source in the presence of a very high local "background."

A similar situation can exist in a scan to locate functioning metastatic thyroid carcinoma. In liver scanning, when the detector is aimed at the boundaries of the liver, the rest of the liver is an interfering source of radiation which should not be recorded.

Examination of many clinical thyroid, brain, and liver scans revealed that detectors were recording more gamma rays that penetrated the shielding than they were recording rays coming from the desired field of view. In other words, the detectors were recording more "noise" than "signal." The study also showed that the apparent size of target organs was greatly increased by lack of septum opacity in the focusing element. This evidence was found chiefly in scans where I^{131} was the gamma ray source.

In scans where isotopes emitting higher-energy gamma rays were employed, penetration of shielding was even more evident. Lead collimators lose their focusing properties at higher energies, therefore, lead collimators limit the investigator in his choice of isotopes to those emitting only low-energy gamma rays.

TABLE 1.

NARROW-BEAM TRANSMISSIONS OF GAMMA RAYS THROUGH VARIOUS MATERIALS,* AND FIGURES OF MERIT FOR THOSE MATERIALS

	Percent transmission through two inches of material		*Relative figure of merit as a gamma ray shield*	
Material	*at 511 kev*	*at 1.3 Mev*	*at 511 kev*	*at 1.3 Mev*
Lead	.017	4.0	1.0	1.0
Mercury	.00528	2.2	3.3	1.8
Tungsten Alloy (17.7 g/cm^3)	.00102	0.76	17.0	5.7
Gold (pure)	.00012	0.44	144.0	9.1

*From mass absorption coefficients taken from C. L. Davisson, *Beta and Gamma Ray Spectroscopy*, edited by K. Siegbahn, North Holland Publishing Co., Amsterdam (1955).

In scanning it is desirable to have a directional detector that will retain its focusing capability even in the field of a strong interfering source, and even with high-energy gamma rays. Therefore, materials other than lead were investigated. Table 1 shows narrow-beam transmissions of gamma rays through several possible shield or collimator materials, and relative figures of merit as shields. (The numbers represent an optimistic view of these metals as shielding materials, since broad-beam transmissions actually obtain. However, the numbers help establish the relative worth of these materials as shields.)

After consideration of Table 1, and after several intermediate attempts which led to collimators not yet as good as desired, (3, 4) the collimator of Fig. 1 was constructed.

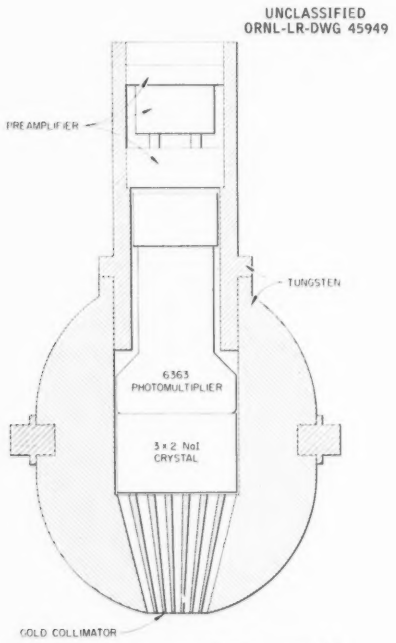

Fig. 1. 3 in. Tungsten Probe assembly

Figures 2, 3, and 4 show the responses in air to point sources of I^{131} (364 kev with 638 kev interfering), Cs^{137} (661 kev), and Zn^{65} (1.114 Mev), respectively. (It is to be pointed out that while point-source responses may or may not be directly useful for clinical purposes, they are direct measures of the directional properties of a collimator-detector assembly.) It is seen that the collimator exhibits a "volume-focus," and that it retains its focusing properties even at high energies. It should be noted that low percentage contours fall close to the axis of the collimator. It is possible to plot the 0.5 percent contour except at the highest energy. The location of these low-level contours are very important in determining the spatial response shown by a collimator. Fig. 2 shows that a point source near the focus of the detector of Fig. 1 but 0.5-inch off axis, will be recorded less than 1/200 as intense as the focus on axis.

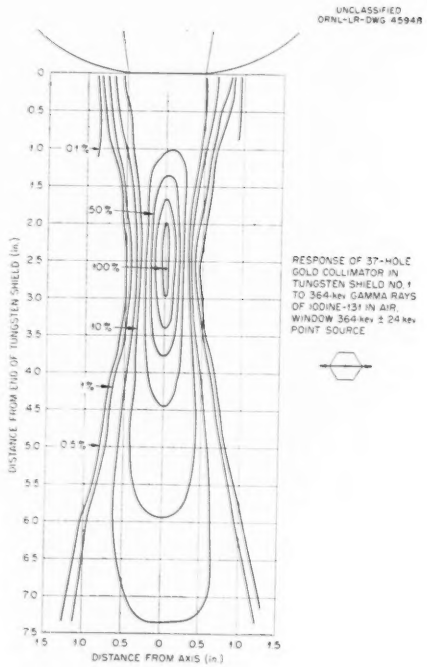
UNCLASSIFIED
ORNL-LR-DWG 45948
RESPONSE OF 37-HOLE GOLD COLLIMATOR IN TUNGSTEN SHIELD NO. 1 TO 364-kev GAMMA RAYS OF IODINE-131 IN AIR. WINDOW 364-kev ± 24 kev POINT SOURCE
DISTANCE FROM END OF TUNGSTEN SHIELD (in.)
DISTANCE FROM AXIS (in.)

Fig. 2

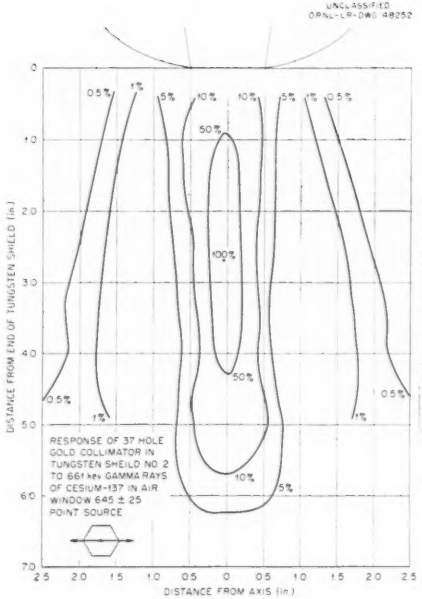
UNCLASSIFIED
ORNL-LR-DWG 48252
RESPONSE OF 37 HOLE GOLD COLLIMATOR IN TUNGSTEN SHIELD NO. 2 TO 661 kev GAMMA RAYS OF CESIUM-137 IN AIR WINDOW 645 ± 25 POINT SOURCE
DISTANCE FROM END OF TUNGSTEN SHIELD (in.)
DISTANCE FROM AXIS (in.)

Fig. 3

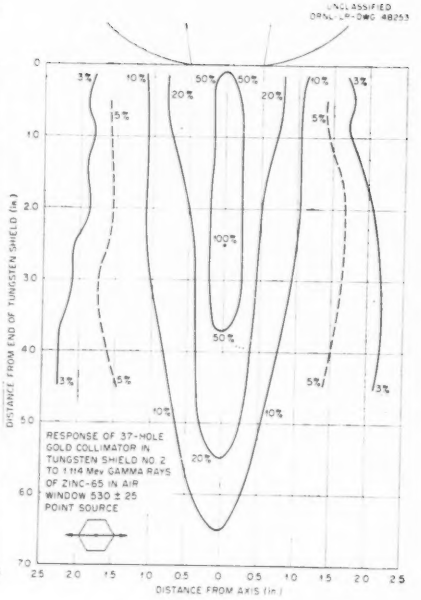
UNCLASSIFIED
ORNL-LR-DWG 48253
RESPONSE OF 37-HOLE GOLD COLLIMATOR IN TUNGSTEN SHIELD NO. 2 TO 1.114 Mev GAMMA RAYS OF ZINC-65 IN AIR WINDOW 530 ± 25 POINT SOURCE
DISTANCE FROM END OF TUNGSTEN SHIELD (in.)
DISTANCE FROM AXIS (in.)

Fig. 4

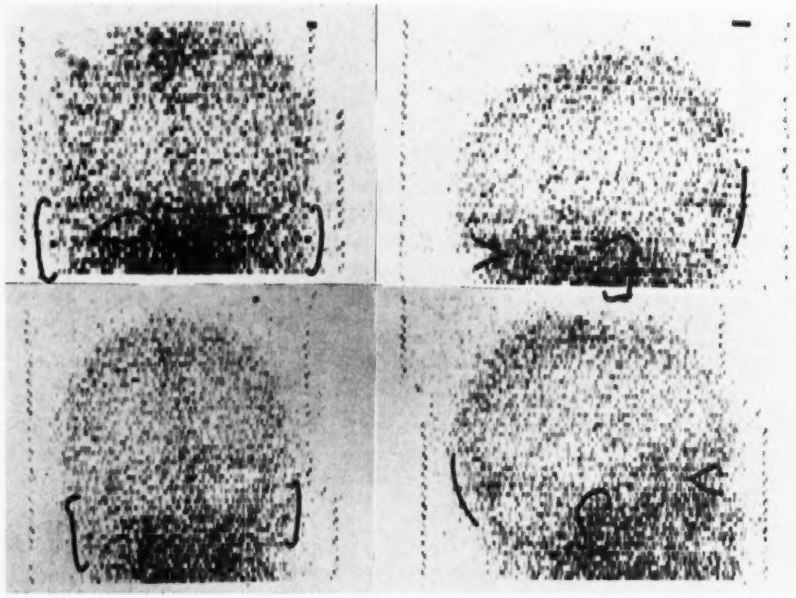

Fig. 5. 5a—upper left; 5b—lower left; 5c—upper right and 5d—lower right.

The collimator has been tested in several clinical situations. Fig. 5 shows head scans of a patient 24 hours after the I.V. administration of 800 microcuries of human serum albumin, tagged with I^{131} (R.I.S.A).

In the anterior-posterior view (Fig. 5a) normal regions of activity are seen at the apex of the skull (superior sagittal sinus), at the periphery of the skull, and at the base of the skull, posterior to the nasion. The posterior-anterior view (Fig. 5b) shows the superior sagittal sinus and the lateral sinus (which, in this case, is larger on the right than on the left). In the right and left lateral views (Fig. 5c and 5d respectively), the uptake in the superior sagittal sinus

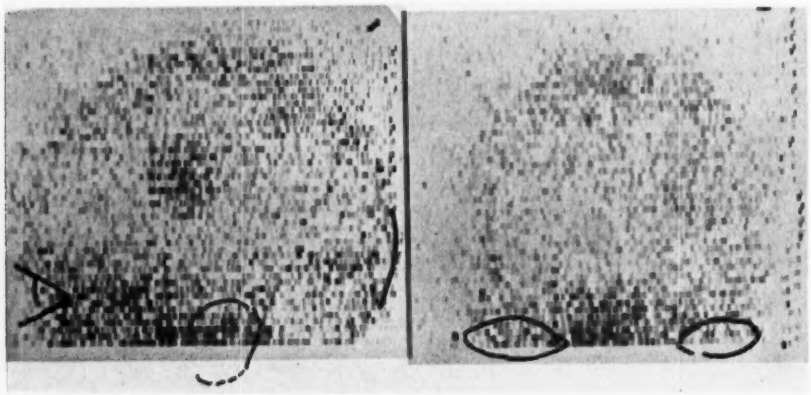

Fig. 6

region appears to increase from anterior to posterior with a maximum apparent at the confluence. These scans, which show good outlining of the skull and major sinuses, are thought to represent a normal patient.

Figure 6 shows the left lateral and AP views of a patient with metastic ovarian carcinoma. One lesion is evident in the left temporal lobe, and a second is seen in the right superior parasagittal region. The size and location of both tumors were confirmed very closely at autopsy.

Figure 7 shows the right lateral view of a patient 24 hours after injection of 600 microcuries of R.I.^{131} S.A. A lesion, clearly delineated in the frontal lobe, was found to be metastatic bronchogenic carcinoma at autopsy.

One clinical situation in which the new detector has been useful is the scanning of thyroid carcinoma patients after massive therapeutic doses of I^{131}. These patients contain so much radioiodine that it his been impossible to scan them with lead collimators until the radioiodine has been largely cleared from the body. This is because penetration of the detector shielding by gamma rays from the patient caused the scans to appear to represent uniform "seas" of activity. It often took a week or ten days for a patient to "cool off" to a point where even a poor scan was obtainable. The new detector assembly is sufficiently well shielded that patient "background" is sharply reduced, and good scans may be obtained only two days after large doses of Iodine-131.

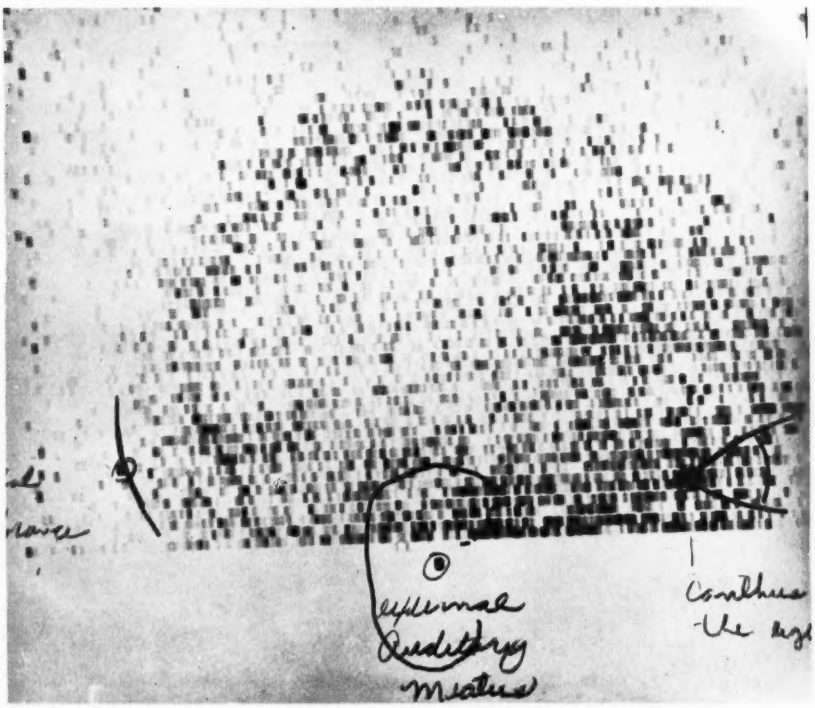

Fig. 7

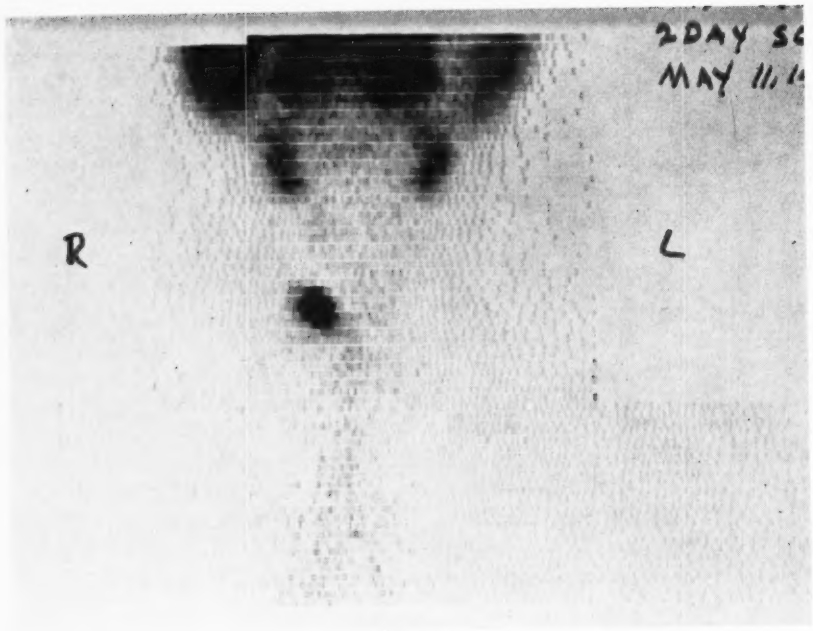

Fig. 8

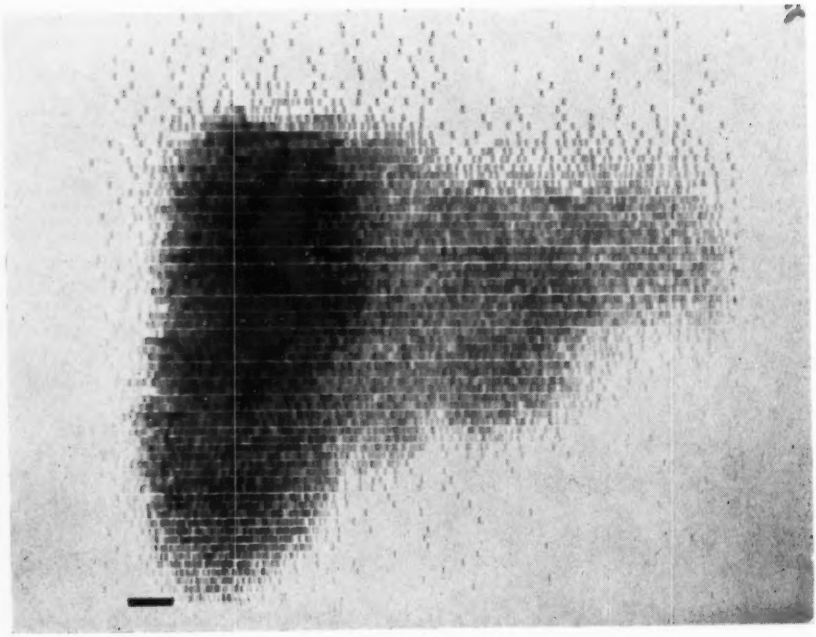

Fig. 9

Figure 8 is a scan taken two days after the patient had received an administration of 5 millicuries of I^{131}. An outline of the patient is seen, as well as pools of activity in the salivary glands and the mouth. A small metastasis is also evident.

The improved shielding of the new detector appears to have alleviated some of the problems in outlining the liver. Figure 9 shows a liver scan after the administration of 180 micro-curies of gold-198.

The ORNL tungsten-gold focusing collimator assembly has been demonstrated, by laboratory and clinical tests, to have a narrowly confined field of response. The regions where response is less than one percent of maximum at focus are very important in clear delineation of target organs. At I^{131} gamma-ray energies, these low-level regions of response lie close to the axis of the new device. Performance at higher energies, while degraded, is much better at high gamma-ray energies than with lead shielding. Higher count-to-background ratios and higher "target-non-target" ratios are observed with the tungsten-gold collimator assembly.

It is believed that the use of tungsten and gold in directional detector assemblies for scanning is justified. Such detectors should offer a new order of detail and utilization of information from the patient. It is also believed that, as better scan recording methods are developed, the advantages of this collimator assembly will become more apparent.

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JOURNAL OF NUCLEAR MEDICINE 3:18, 1962

Therapy of Polycythemia Vera With Radioyttrium (Y-90)[1,2]

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Polycythemia vera is presently treated by phlebotomy, external spray radiation, radiophosphorus and chemotherapeutic agents such as TEM.

Radioactive yttrium (Y^{-90}) is a radiometal with ideal characteristics for systemic clinical therapeutic application. It is a 2.18 Mev pure beta emitter with a half life of 61 hours, and can be shipped to laboratories at a distance from the production site without great loss of radiation strength. Like the rare earth group of elements to which it bears chemical similarity it forms insoluble complexes with nucleic acids and has a strong affinity for chelating agents.

In previous studies Greenberg and Dudley have shown that the deposition and metabolic fate of a metal can be altered and controlled by manipulation of the chelating agent with which it is combined (1-5). These compounds have the ability to combine with metal ions, to form cyclic complexes which are water soluble and virtually undissociated. Because of this feature these substances can completely change the properties of ions in solution, and by the proper manipulation of one or more of these materials considerable chemical control over cations in solution can be achieved (in vivo as well as in vitro).

By using this principle we have been able to achieve *significant selective localization* of systemically administered Y-90 in a number of organs in animals and man including the bone, marrow, liver, spleen, lymph nodes and gastric mucosa (4, 5).

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1. Presented at the Seventh Annual Meeting of the Society of Nuclear Medicine, June 23, 1960, Estes Park, Colorado.

2. From the Divisions of Nuclear Medicine and Hematology, The Long Island Jewish Hospital, New Hyde Park, N. Y. Supported by grants from the Leukemia Society, and The Harvey Sesskin Memorial Fund.

3. Current Address: Professor and Director, Department of Nuclear Medicine, the New York Polyclinic Medical School and Hospital, New York City.

In 1957 we reported studies with rabbits and dogs which showed that Y-90, chelated with an excess of N'hydroxy ethylenediamine triacetic acid (Ed-ol) and at a low carrier dose ($\curvearrowright$0.05 mg Y-89/Kg body wt.), will localize selectively in the skeleton following systemic administration (6). The energetic beta emission irradiates the adjacent marrow and induces predictable and controllable hematologic changes.

We have since reported on the use of this radiometal in leukemia and multiple myeloma (7, 8). Our experience in these diseases suggested that this modality might prove to be a valuable agent in the therapy of polycythemia vera. Among the theoretical advantages of Y-90 over P-32 are its shorter half life (61 hours as compared to 14.3 days) and the preferential localization of the chelated Y-90 in bone, making possible a larger dose of internal radiation to the tumor site with minimal systemic effects.

MATERIALS AND METHODS

To date nine patients with known polycythemia vera have been treated with Y-90. Of these, one expired in congestive heart failure 10 days post therapy and will not be included in the evaluation of this series. The other eight have been followed from 5 to 17 months. There were six males and two females, with ages from 53 to 84 years (Table 1).

At the time of diagnosis the red cell counts ranged from 7-10.5 million/cmm, the hemoglobins from 17-23.5 gm. per cent and the hematocrits from 56-79 per cent. The white cell counts varied from 10,000-23,000/cmm and the platelet counts from 0.5- $>$ 3.0 million/cmm.

Duration of disease prior to Y-90 therapy was 2 months to 6 years. Six of the patients had 1 to 5 doses of P-32 from 1 to 6 years prior to Y-90 and one (F. C.) received TEM intermittently during a 2 year period which preceded his Y-90 therapy by 4 years. Only one patient (J.S.) received P-32 in the year prior to Y-90 therapy, but was essentially nonresponsive. Two patients received no specific previous therapy.

Seven of the patients were phlebotomized within the 2 months immediately preceding Y-90 therapy in amounts from 500-4400 mls.

At the time of therapy the red cell counts ranged from 6-9.5 million/cmm, the hemoglobins from 14-17.5 gm. per cent and the hematocrits from 50-62 per cent. The white cell counts varied from 6,000-23,000/cmm and the platelet counts from 350,000- $>$ 1 million/cmm.

Iron deficiency patterns were induced in two patients (B.L. and H.W.) by repeated phlebotomies totaling 2750-4400 mls.

In five of the seven patients being followed clinically there was significant hepatosplenomegaly. One patient showed only hepatomegaly and one only splenomegaly. The 8th patient was confined to his home because of senility and only blood counts were obtained, without the benefit of clinical observation. Among the symptoms present prior to therapy were easy fatigability, pruritis, dizziness, headache, irritability, and epistaxis.

TABLE 1. STATUS OF PATIENTS BEFORE THERAPY WITH CHELATED RADIOYTTRIUM (Y-90)

Pt.	*Age*	*Sex*	*Prev. P-32*	*Date*	*Dose (mc)*	*Response*	*Duration (months)*	*Diagnosis to Y-90 (months)*	*Blood ↓ in 2 months before Y-90 (ml)*	*Comment*
B.L.	72	F	Yes	1956	Unk.	Unk.		36	2750	
				1957	Unk.	Unk.				
D.M.	74	M	Yes	Oct. 1957	4.1	No		16	500	
				Feb. 1958	4.7	Yes	12			
J.S.	65	M	Yes	July 1958	4.4	No		11	1000	
				Oct. 1958	4.8	No				
F.C.	73	M	Yes	Mar. 1956	4.0	Yes	12	72	500	1953–55
				Dec. 1957	4.2	Yes	15			TEM
W.T.	53	M	Yes	1953	Unk.	Unk.		72	1500	
				1955	Unk.	Unk.				
				Sept. 1957	4.0	No				
				Mar. 1958	4.3	No				
				July 1958	5.0	Yes	12			
H.W.	58	M	No					2	4400	
B. R.	68	M	No					1	3000	
B.W.	84	F	Yes	Apr. 1957	4.0	Yes	32	36	None	

TABLE 2. EFFECTS OF THERAPY WITH CHELATED RADIOYTTRIUM (Y-90)

Pt.	*Date Given*	*Dose Given*		*Dose %*	*Dose Retained*		*Spleen (cm ↓ LCM)*		*Liver (cm ↓ RCM)*		*Side Effects*	*Time Since Therapy (months)*
		mc/Kg	*mc*		*mc/Kg*	*mc*	*Before*	*After*	*Before*	*After*		
B.L.	1–15–59	0.25	10.8	93	0.23	10.0	2	0	2	0	Epistaxis	17
D.M.	2–12–59	0.25	18.4	69	0.17	12.7	4	0	1	0	None	16
J.S.	4–23–59	0.20	13.0	85	0.17	11.0	0	0	2	at CM	Petechiae	14
F.C.	5–22–59	0.20	16.4	83	0.17	13.6	–	–	–	–	None	13
W.T.	9–10–59	0.20	16.0	92	0.18	14.7	1	at CM	at CM	at CM	Petechiae	9
H.W.	11–19–59	0.18	14.0	78	0.14	10.9	6	at CM	2	at CM	Petechiae	7
B.R.	12–31–59	0.18	11.5	81	0.15	9.3	5	2	3	0	None	6
B.W.	1–14–60	0.10	6.0	93	0.09	5.6	4	0	2	0	None	5

The preparation of the yttrium chelate and the counting procedures have been described in previous publications (4, 5).

The radioactive isotope was administered intravenously as a single dose of radioyttrium chelated with an excess of Ed-ol and containing 0.05 mg Y-89 per kilogram as carrier. The individual dose varied from 0.10 mc/Kg to 0.25 mc/Kg. Urine was collected over the next 72 hours and the quantity of Y-90 excreted was measured. The amount of Y-90 retained varied from 69-93% of the dose given, with an average of 84 per cent. The actual dose delivered varied from 0.09 mc/Kg to 0.23 mc/Kg (Table 2).

RESULTS

Post therapy all 8 patients showed a fall in hemoglobin and hematocrit of 2-6 gm. per cent and 12-23 per cent respectively (Fig. 1). Red cell counts fell from 1.5 to 4 million/cmm. The maximum fall of erythroid elements usually occurred at about 3 months post therapy. The lowest levels reached by the erythroid components were 10.5 gm. per cent Hgb., 3.5 million RBC/cmm and a hematocrit of 30 per cent. This patient (B.W.) received the smallest dose (0.10 mc/Kg), but was also the oldest (84). Leukocytes fell to levels of 3000-1300 WBC/cmm in 6 patients, the maximum decline being 3-8 weeks post therapy. No infections

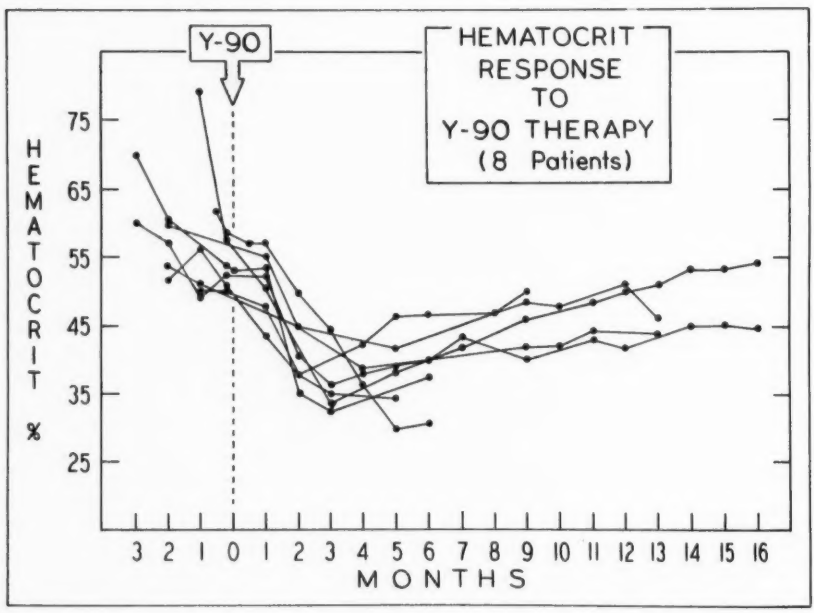

Fig. 1

occured during the period of leukopenia. Maximum fall in platelets occurred in 3-8 weeks, reaching levels below 100,000 in 2 patients. Concomitant with this, transient petechiosis and easy bruisability was noted in 3 patients while one patient had severe epistaxis. Recovery was spontaneous in all cases. Leukocyte and platelet counts returned to and have stayed at normal levels in 8-16 weeks post therapy. Where the liver and spleen were enlarged they regressed significantly in all instances after treatment (Table 2).

In the 7 patients in whom the erythroid components fell below normal levels 5 have returned to and stayed at essentially normal levels 3-7 months post therapy. In the other 2 (B.W. and B.R.) these components are first beginning to rise toward normal 5 and 6 months post therapy respectively.

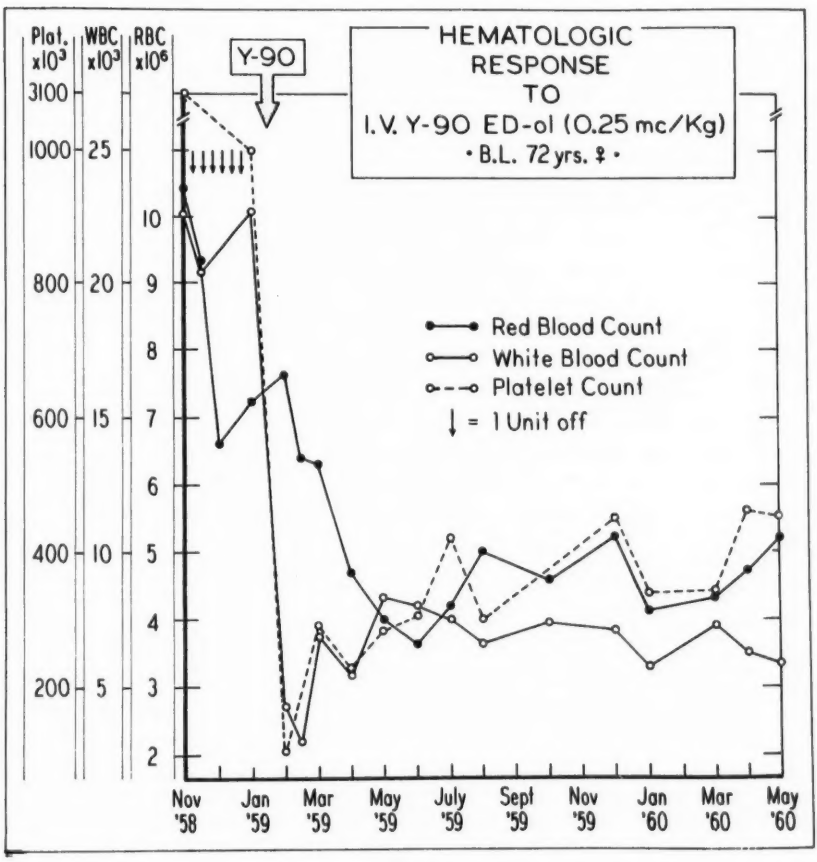

Fig. 2

Since the hematologic responses were qualitatively similar in all cases these can be summed up by using the first case treated as a prototype (Fig. 2).

One patient (D.M.) had an excellent remission which lasted 16 months. He has recently become symptomatic (fatigue) with returning hepatosplenomegaly and rising erythroid components and has just had 1 phlebotomy. This patient required 8.8 mc P-32 in 4 months to get a 12 month remission.

One other patient (W.T.) went from considerably elevated baseline counts to essentially normal levels, but at 9 months post therapy is beginning to show an enlarging liver and spleen and rising peripheral counts. He is still asymptomatic. This patient required 13.3 mc of P-32 in 10 months in order to get a remission which lasted 12 months.

The other six patients are all completely well at this time and are in excellent remission, both clinical and hematologic, the longest being 17 months.

DISCUSSION

This investigation stemmed from data previously obtained by Greenberg and Dudley which show that Y-90, chelated with an excess of N'hydroxy ethylenediamine triacetic acid (Ed-ol) and at a low carrier dose ($\backsim$ 0.05 mg Y/Kg body wt.), will localize selectively in the skeleton (5). The energetic beta emission irradiates the adjacent marrow, causing selective destruction or at least a marked reduction in its potential to produce immature or bizarre forms of the cellular elements of the blood (6-8). The relatively short half-life of the Y-90 permits good control of radiation dosage. A further safe guard is the ease with which yttrium may be cleared from the body should too high a dose level be established. Thus, intravenous administration of a chelate such as Ca-EDTA, a standard pharmaceutical preparation, promotes rapid clearance of yttrium via the kidney.

The data thus far obtained point towards the potential usefulness of this modality in the therapy of polycythemia vera. Careful titration of the dose of Y-90 administered makes it possible to effect preferentially the various components within the marrow, and hence the peripheral blood. It is also possible that other neoplasms involving the marrow and/or bone (primary or secondary) may be effected in a salutory manner with the proper manipulation of the dose of Y-90 given.

SUMMARY

Nine patients with polycythemia vera have been treated from 5-17 months ago with a single intravenous injection of chelated radioactive yttrium (Y-90) in dosages ranging from 0.10 to 0.25 mc/Kg of body weight. An excellent response, both clinical and hematologic, has been obtained in all the patients. This includes relief of symptoms, regression of organomegaly, and normalization of the hematologic picture. Two of these patients, treated 16 and 9 months ago, may possibly be going into relapse. The others are continuing in essentially complete remission. Toxicity was limited to transient petechiosis and epistaxis, from which recovery was spontaneous.

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Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the March, 1962 issue must be in the hands of the Editor before February 1, 1962.

JOURNAL OF NUCLEAR MEDICINE 3:26, 1962

The Orins Linear Scanner in Clinical Diagnosis[1,2]

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Marshall Brucer, M.D.
A. C. Morris, Jr., M.S.E.
Ruth Black, R.T.

We have defined linear scanning in a previous presentation (1) as a method by which a continuous recording of count rate is obtained by moving radiation detectors along the body, producing a curve in which every point on the curve represents count rate versus position on the long axis of the body. In other words, it draws a profile of radioactivity present in a patient's body (Fig. 1).

This method was first introduced in clinical investigation by E. E. Pochin in England in 1954 (2). He uses a Geiger Muller tube with a sensitive volume of 8.5 cm long and calls it profile counting. J. P. Concannon of Chicago modified the method by using a scintillation detector with a lead collimated head with a transverse wedge-shaped slit (3). He calls it total body scanning.

The ORINS linear scanner represents an elaboration of these earlier instruments (Fig. 2). It has 12 scintillation probes, each equipped with a two-inch sodium iodide crystal. The probes are mounted linearly in two units, six in each, between collimating lead lips two inches thick. The crystals face each other in a vertical plane, which is perpendicular and transverse to a table on which the patient is positioned. This table is motor driven and moves between these two detector units at a constant speed. Each one of the crystals is attached to a photomultiplier tube with a modified preamplifier. All 12 probes are connected to one medical spectrometer, which has a recorder connected to it. This machine was originated by M. Brucer, was designed by D. Ross and A. C. Morris, Jr., all of the Medical Division of the Oak Ridge Institute of Nuclear Studies (ORINS), with the assistance of J. E. Francis and C. C. Harris of the Oak Ridge National Laboratories (ORNL); and it was built in the ORINS Shop (4). The

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[1]Work done at the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission.

[2]Acknowledgement is made to Dr. W. H. Beierwaltes for his help in the preparation of this manuscript.

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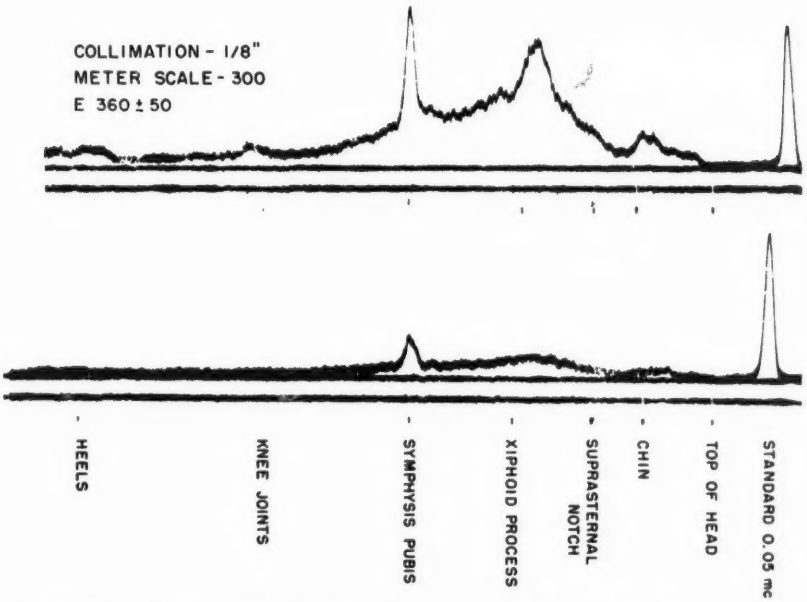

Figure 1. Iodine-131, 24 and 48 hours after oral administration to a patient without evidence of functioning thyroid tissue.

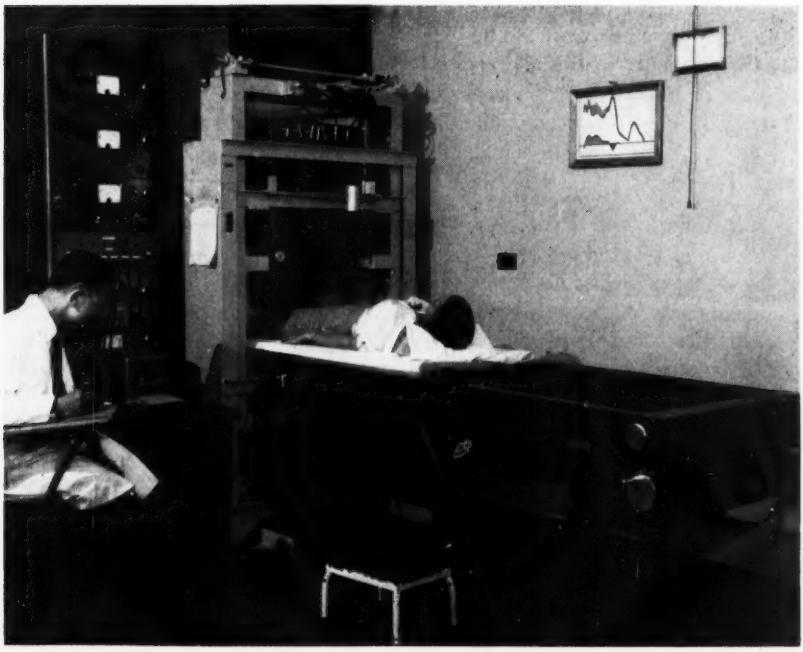

Figure 2. The ORINS linear scanner.

important changes in the ORINS linear scanner, in comparison to the earlier instruments are:

1. Increased sensitivity
2. Adjustable and more efficient collimation
3. Positioning of two detector units opposite each other, recording count rate over the ventral and dorsal aspects of the patient simultaneously, reducing the effect of the absorber, i.e., body tissue.

The purpose of this presentation is to determine the usefulness of linear scanning in general, and of the ORINS linear scanner in particular, in clinical diagnosis using various radioisotopes.

METHOD

The technique is the same used in a previous study (1), except for the standard, which now represents an aliquot of the administered radioisotope with an activity of from 0.01 to 0.1 millicuries placed in a test tube, instead of 0.05 millicuries of mock iodine.

RESULTS

This study was conducted at the Medical Division of the Oak Ridge Institute of Nuclear Studies over a period of five months. Linear scans were made of every suitable patient who had received a radioactive isotope in the process of diagnosis or treatment or both. Ten radioisotopes and an additional four radioiodinated compounds were studies for their distribution in 49 patients (5). Five of twenty patients who had thyroid carcinoma were discussed previously (1). The scans of 10 patients who had been studied with arsenic-74, copper-64, iodine-131 diodrast, gold-198, yttrium-90, and sodium-24 are presented here.

Arsenic-74

This radioisotope is used for localization of brain tumors. 0.5 millicuries of arsenic-74 were given intravenously to a patient who was suspected of having a brain metastasis from a bronchial carcinoma. Figure 3 shows three linear scans, made at 35 minutes, 8 hours, and 20 hours after administration of the dose. In the first scan, the activity appears to be carried in the circulation as suggested by the elevations of the curve in cross sections where pooling of blood occurs and is accumulated at the level of the upper abdomen and of the symphysis pubis, recording the event of the renal clearance from the blood and the urinary excretion. At 8 hours, the activity in the circulation has greatly decreased and a shift of the former renal peak headwards has occurred, compatible with the storage of arsenic-74 in the liver. This process has progressed further in the 20-hour scan. No uptake was found in the skull.[1]

[1]An A P and right and left lateral scan of the skull, performed by J. E. Francis and C. C. Harris of ORNL with a three-inch crystal and combined mercury-gold honey-comb collimator also failed to demonstrate localization of arsenic-74.

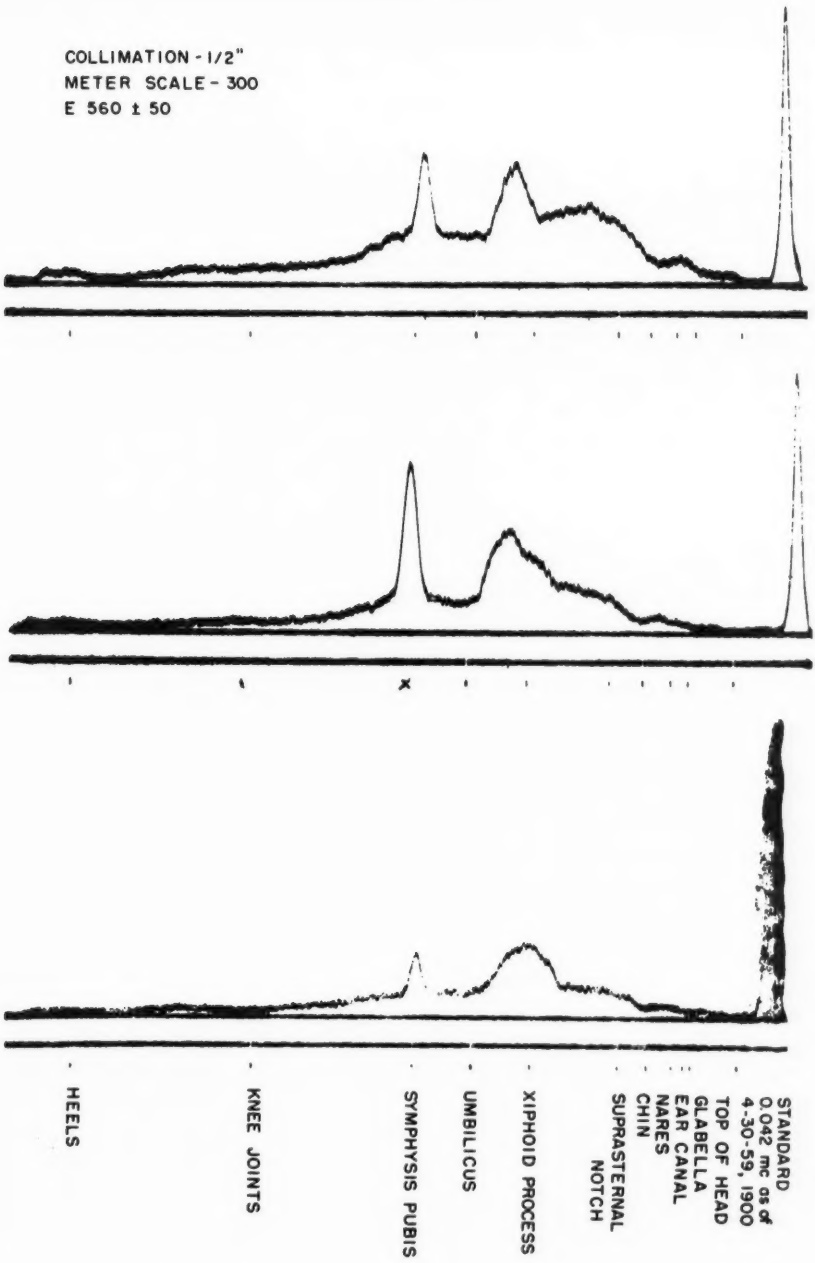

Figure 3. Arsenic-74, 35 minutes, 8 hours, and 20 hours after intravenous administration (from top to bottom).

Copper-64

Similar events were observed in a series of linear scans of a patient who had received 0.5 millicuries of copper-64 EDTA chelate intravenously. At 15 minutes, the radioactivity is distributed throughout the circulation and renal clearance and urinary excretion can be recognized by the above described elevations in this curve (Fig. 4). Additional studies showed that the renal clearance of copper-64 was slower than that of arsenic-74.

Iodine-131 diodrast

This compound is known for the rapidity with which it is cleared by the kidneys. A linear scan done within the first 10 minutes after the intravenous injection of 0.5 millicuries of radioiodinated diodrast shows most of the radioactivity already at the kidney level while an appreciable amount is still visible in the circulation. The linear scan at 60 minutes, which is presented in Figure 5, shows most of the radioactivity at the level of the urinary bladder, reduced activity at the kidney level, and almost none in the circulation.

Gold-198

At the Medical Division of ORINS, colloidal gold-198 is used intracavitarily for treatment of effusions caused by neoplasms, and intravenously for treat-

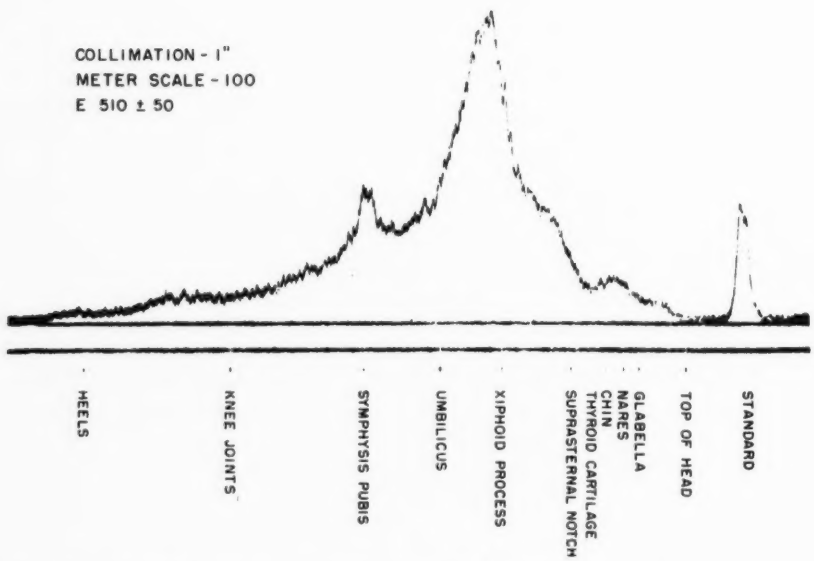

Figure 4. Copper-64, 35 minutes after intravenous administration.

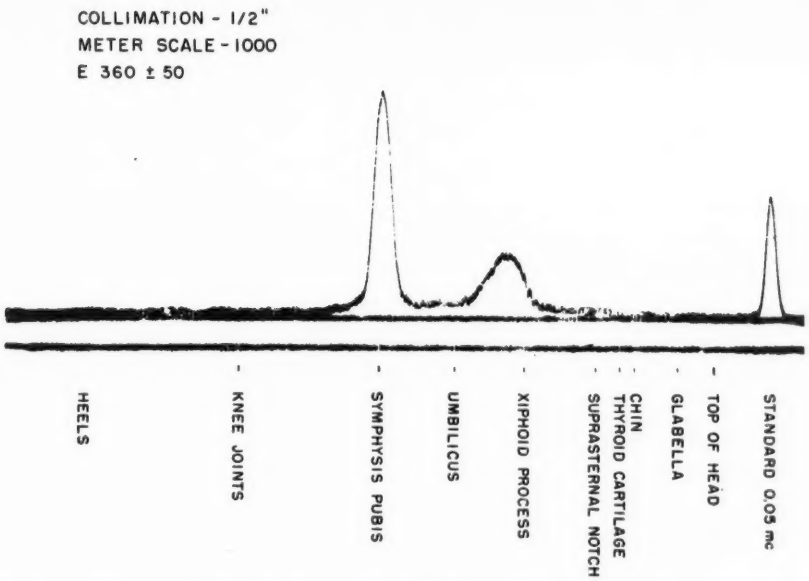

Figure 5. Iodine-131 diodrast, 60 minutes after intravenous administration.

ment of chronic granulocytic leukemia. Figure 6 shows a linear scan of a patient with recurrent pleural effusion from Hodgkin's disease 8 days after administration of 98 millicuries of radioactive colloidal gold to the right pleural cavity. If one extrapolates the slopes of the peak onto the base line, the activity extends from 2 cm above the suprasternal notch down to 8 cm below the xiphoid process, covering as much of the longitudinal axis of the patient's body as we expect a projection of the pleural cavity would cover. This indicates a good resolution of the instrument, particularly in view of the high dose. For comparison we have scanned a patient with recurrent pleural effusion from a breast carcinoma, who had received 20.1 millicuries of yttrium-90 to the right pleural cavity four days after administration of the dose (Fig. 7). The extrapolated peak of radioactivity covers 32 cm of the base line, which checked with the length of the patient's thorax. This suggests that the instrument can be used for study of pure beta emitters.

The linear scan in Figure 8 was made 8 hours after the intravenous injection of 3.3 millicuries of gold-198 to a patient who had thrombocytopenic purpura. This was an attempt to determine whether or not the patient had an accessory spleen, when he failed to improve after a splenectomy. The prominent peak in this linear scan is located in the lower chest and upper abdomen and was identified by an area scan as uptake of gold-198 in the liver. The distribution of the activity outside the liver is recorded in profile humps; one is located in the chest, one with a dromedary hump appearance

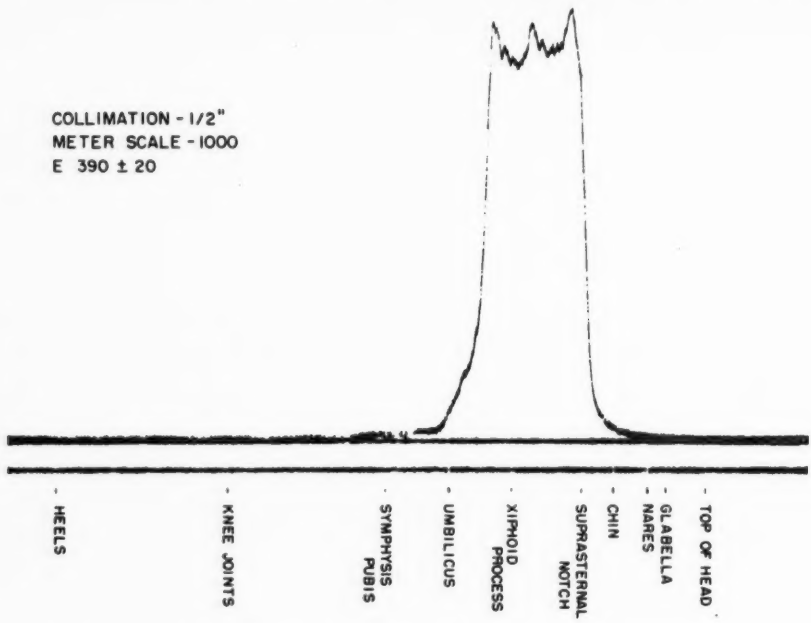

Figure 6. Gold-198, 8 days after administration to the right pleural cavity.

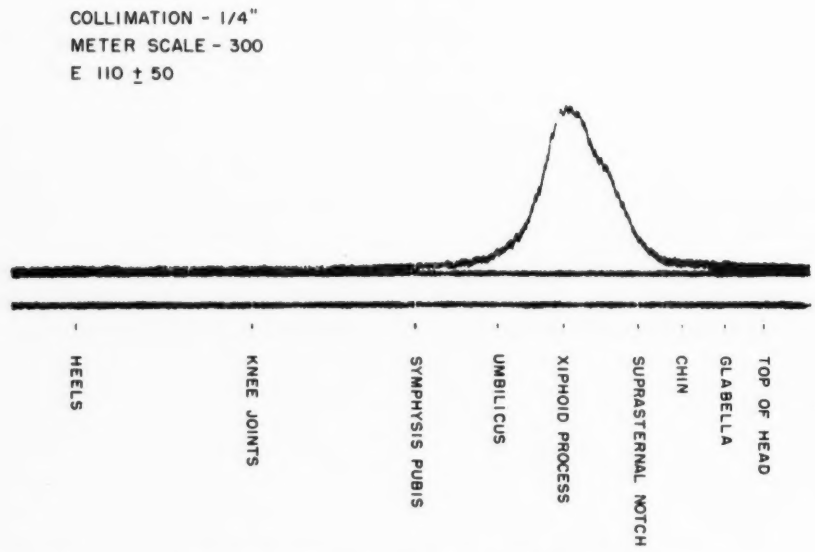

Figure 7. Yttrium-90, 4 days after administration to the right pleural cavity.

in the lower abdomen, one at the level of the knees, and one at the feet. Postulating that the extrahepatic activity represents uptake in the reticuloendothelial system of the bone marrow, this distribution of gold would confirm it, because in these same parts of the body expansions of the bone marrow spaces occur physiologically. If our hypothesis is correct, linear scanning then would provide us with a method of gross determination of bone marrow function or space, or both.

We also had the opportunity to study a patient with chronic granulocytic leukemia who had received a total of 110 millicuries of gold-198 in a period of three years. The linear scan in Figure 9 was obtained 24 hours after the administration of 14.6 millicuries of radioactive colloidal gold intravenously. The pattern of distribution is similar to the distribution in Figure 8, with the exception that the postulated bone marrow activity is lower in this case. As a matter of fact, the ratio of intrahepatic versus extraphepatic activity is 76.5 to 23.5 in Figure 8 and 78.34 to 11.66 in Figure 9.[1] The difference might be due to the absence of the spleen in the previous case, or to bone marrow damage from previous radiation in the second case.

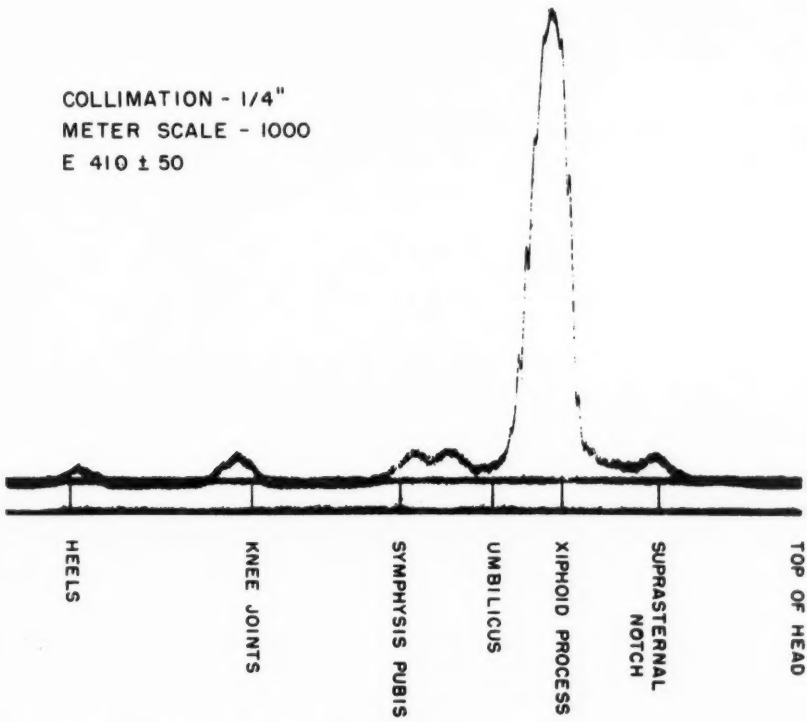

Figure 8. Gold-198, 8 hours after intravenous administration.

[1]The ratio was calculated by measuring the areas under the curve with a Dietzgen planimeter.

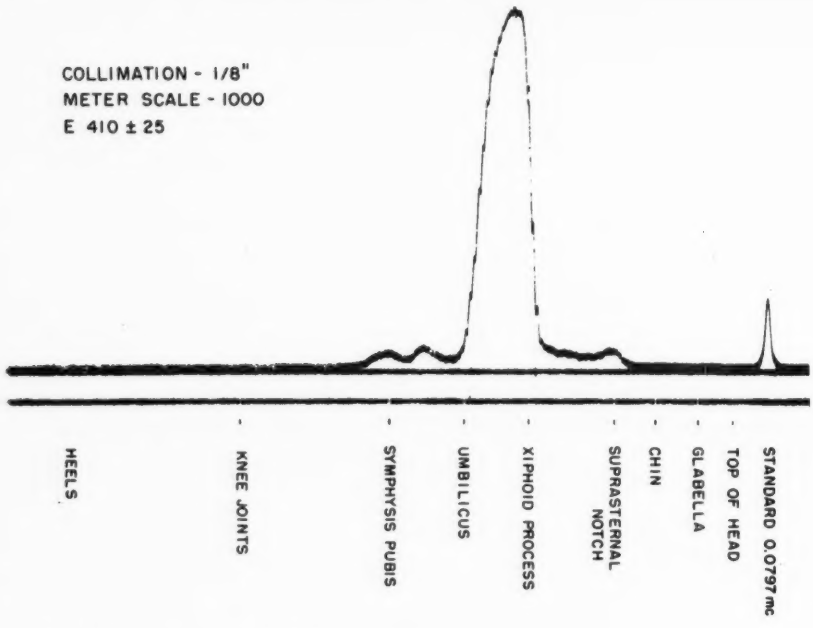

Figure 9. Gold-198, 24 hours after intravenous administration.

The patient whose linear scan is shown in Figure 10 has an unusual medical history which will have some bearing on the interpretation of the scan. She became ill with polycythemia vera in 1948 and was treated with phosphorus-32, totaling 28 millicuries in the period between 1951 and 1955. The amount of phosphorus-32 she received before 1951 is not known. She developed myelofibrosis, first recognized in 1955, and hemolytic anemia, which finally necessitated splenectomy in 1958. Histological sections of the spleen showed diffuse myeloid metaplasia. Because of the appearance of clinical features of chronic granulocytic leukemia, therapy with radioactive gold was initiated. The linear scan in Figure 10 was obtained 28 hours after intravenous administration of 20.6 millicuries of gold-198. This scan can be divided into three areas:

The first represents radioactivity in the upper half of the chest and is bound by the profile curve of this part of the body and by the extrapolated cranial slope of the liver peak;

The second is the area which is covered by the liver peak and its extrapolated slopes; it represents radioactivity in the patient's liver;

The third is the area under the remaining parts of the curve and represents, according to our hypothesis, uptake in the bone marrow.

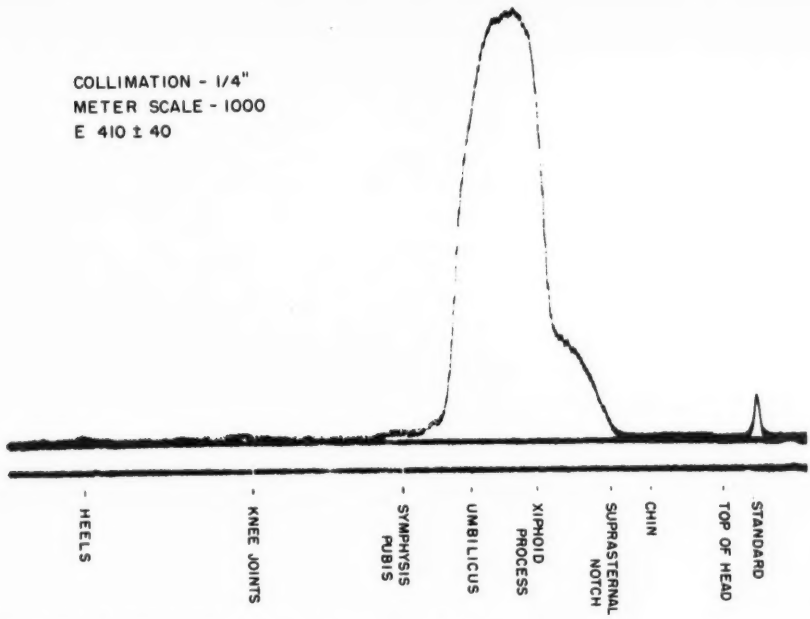

Figure 10. Gold-198, 28 hours after intravenous administration.

The uptake in the liver was very prompt as shown in Figure 11 where the total areas under the curve and the areas under the liver peak were plotted against time in a series of scans. From this graph the effective half life of radioactive gold in the patient's liver was calculated as 50 hours (the physical half life of gold-198 is 65 hours). The ratio of activity in the liver to activity in the lungs to postulated activity in the bone marrow is 88.3 to 9.7 to 1.9. Thus, this patient has the lowest value for bone marrow of all three patients studied with intravenous gold. Whether this is due to the myelofibrosis or uptake in the lungs or size of the liver, which extended into the lower abdomen and into the left upper quadrant, is a decision which must be deferred until more data of this kind are available.

Sodium-24

On June 16, 1958, eight persons were exposed to ionizing radiation from an accidental nuclear excursion in the Y-12 plant at Oak Ridge. Figure 12 shows a series of scans on one of the victims who had received an estimated dose of 356 rads. The activity profile presumably represents sodium-24 produced through neutron bombardment of the stable sodium-23 of the body. The decrease of activity in the scans from day to day is compatible with the effective half life of sodium-24, the physical half life of which is only

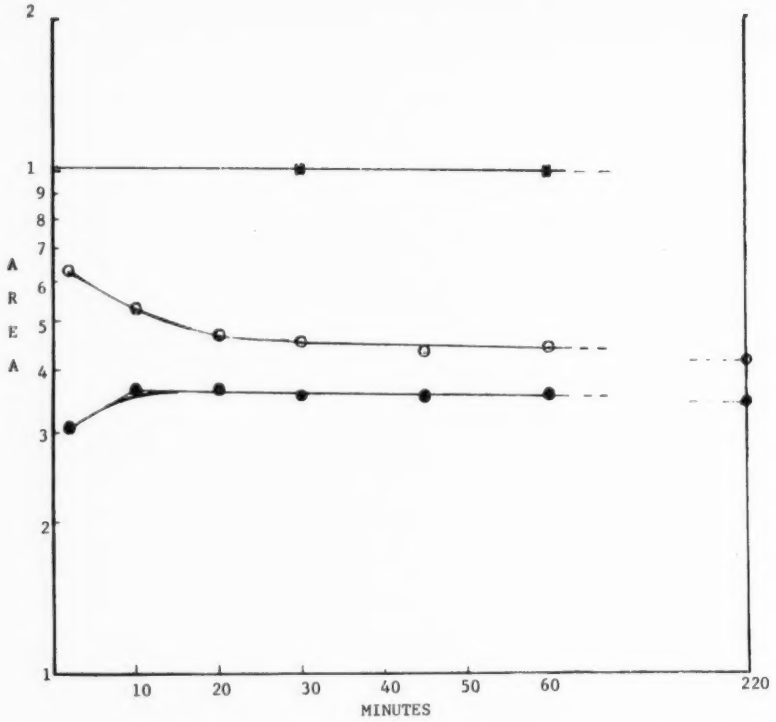

Figure 11. Determination of effective half life of gold-198 in the whole body (o) and in the liver (•) of a splenectomized patient. The curve of the latter also gives rate of uptake, magnitude of uptake, and time of maximum uptake. For comparison the physical half life of gold-198 has been graphed also (top curve).

fifteen hours. An interesting sidelight in this study was the appearance of initially unexplained peaks in the scans of two of the other victims which later on were found to be caused by a gold tooth in the denture of one patient, and a gold ring on the hand of the other patient. The neutrons had activated the stable gold-197 to radioactive gold-198.

For the purpose of comparison, Figure 13 shows a linear scan of a patient three hours after intravenous injection of 0.5 millicuries of sodium-24. The scan profiles the distribution throughout the patient's body in physiological proportions. But this scan is revealing in another sense: It shows that the collimation of 2-inch lead is not adequate for the hard gammas of sodium-24 (2.754 and 1.368 Mev), because the difference in activity between the patient's head and the patient's feet made zero adjustment of the rate meter impossible.

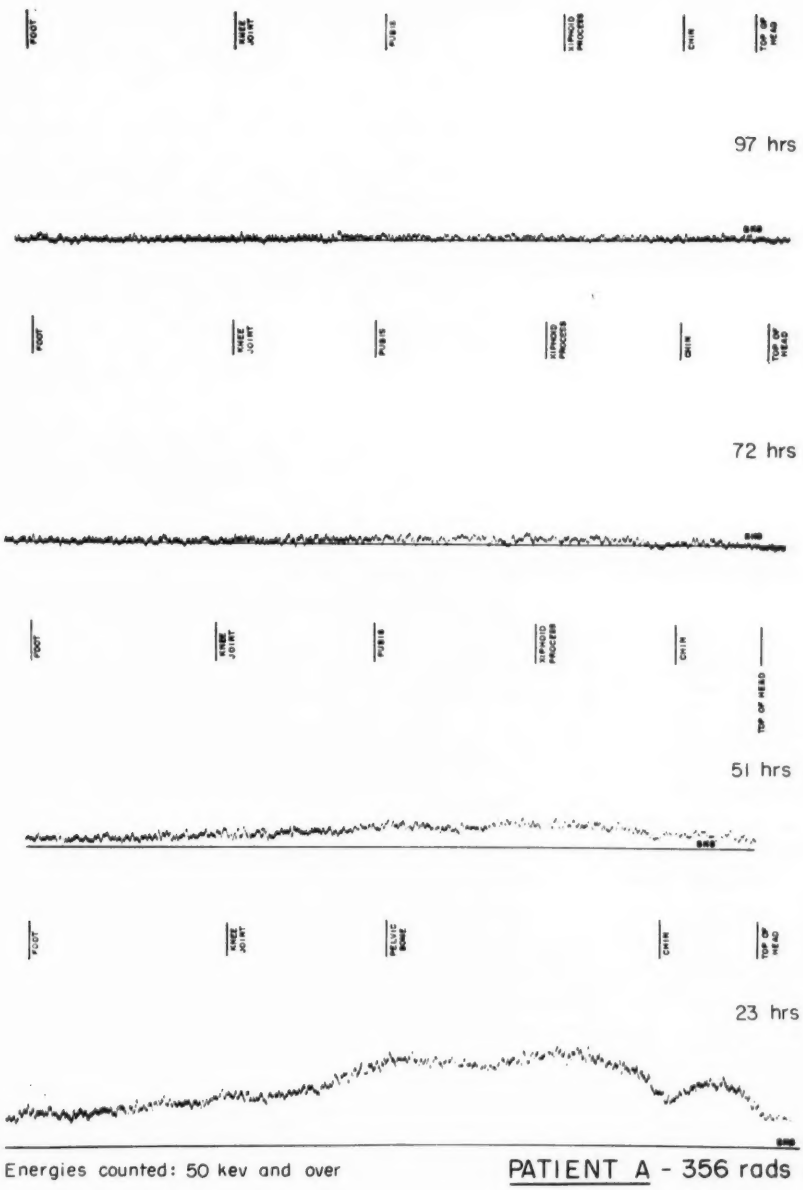

Figure 12. Series of 4 scans of a patient exposed to ionizing radiation from an accidental nuclear excursion. The activity represents neutron activated sodium-23.

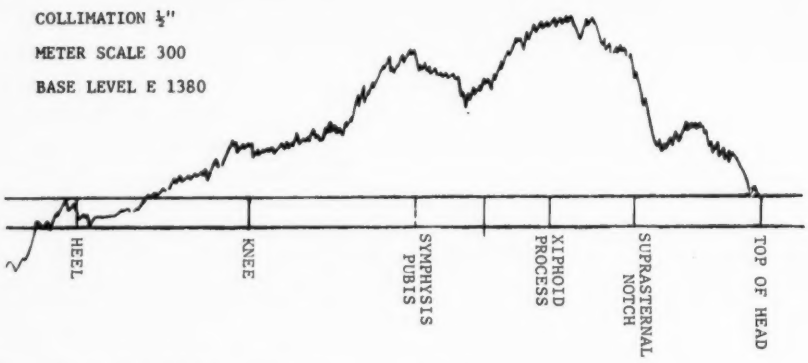

Figure 13. Sodium-24, 3 hours after intravenous injection.

DISCUSSION

From the results presented in the preceding paragraphs and from additional studies carried out with other radioisotopes (1,5), we have observed a number of possible applications of the ORINS linear scanner in clinical work.

With the increasing use of radioisotopes, accidental contamination will undoubtedly increase in frequency. The detection of neutron activated gold objects on the outside and inside of the Y-12 radiation victims indicates that external and internal contamination with radioactive substances could be detected and localized as readily. The same principle applies for therapeutically administered radioisotopes in localized areas such as radioactive gold injected intracavitarily. Here the instrument serves as a control rather than a detector.

A number of radioisotopes are used diagnostically for their participation in metabolic processes, such as radioiodinated diodrast and rose bengal, while others such as arsenic-74 and copper-64 behave in a similar fashion but are used for other than functional studies. All of these isotopes can be conveniently studied with the linear scanner, if repeated scans are obtained, for their metabolic fate such as renal clearance, urinary excretion, storage in the liver, and others.

We have previously said that the ORINS linear scanner draws a profile of the activity of the whole body, which means it not only tells where in the body a radioisotope is located, but also the amount. We have explored several possibilities to use this quantitative information (1) and have found the following method useful. Several scans are obtained after the administration of an isotope at proper time intervals. The total area under each of these curves is then plotted against time on semilogarithmic paper (Fig. 11). The curve resulting from this plot is a function of the effective half life of the radioisotope in reference to the whole body. The area at zero time, which is the equivalent of the administered dose, can be obtained by extrapolating the curve back to zero time. We also plot areas under certain parts of the profile curves against time whenever this area can be attributed to uptake in an organ such as the liver, or a tissue such as a metastasis from a differentiated thyroid carcinoma. The resulting

curve then tells us the rate of uptake and the amount of uptake which can be expressed in percentage of the whole body activity at the time, or in percentage of the administered dose; it also gives us the time of maximum uptake and the rate of activity loss in this area, which in essence is effective half life of the isotope in the area under consideration, such as liver or metastasis (that is, the time at which a 50 per cent reduction in activity has occurred).

All these data are valuable for the clinician. The uptake expressed in percentage of whole-body activity gives us information about the ratio of concentration or ratio of uptake between different organs, such as the ratio between extramedullary and medullary activity of the reticuloendothelial system using gold-198 in one patient, or the ratio of activity in different patients such as medullary activity in one patient versus another (Figs. 8 and 9). Uptake in percentage of administered dose in an organ or certain cross section is a very frequently demanded clinical information, that the conventional uptake method cannot supply most of the time, because it requires the use of a phantom that meets the criteria of geometry and absorber in which the organ is situated. With the linear scanner it is made possible because a phantom is not necessary, the patient is his own phantom. But difficulties still exist even here when it is to be decided how much of the area of the scan is to be attributed to this metastasis or this organ. The determination of effective half life with the linear scanner offers an advantage by not only delineating different exponential components in the plotted curve when they occur, but also by demonstrating the proportions and the locations of elimination, such as urinary excretion.

The method of quantitation discussed above requires the use of total area under the scan, which is the equivalent of a whole-body count. This does not, however, imply that the ORINS linear scanner is a whole-body counter. But it can be used as such if one is willing to sacrifice localization and resolution for total body counts, by widening the collimator opening.

CONCLUSIONS

The ORINS linear scanner has proved to be a useful addition to nuclear instrumentation in clinical investigation. It represents an improvement over earlier instruments by increasing the area of detection sensitivity, by improving the efficiency of collimation, and by using a medical spectrometer. It profiles the radioactivity within the patient, it scans the whole body in ten minutes, and offers some hope of obtaining quantitative data. These properties indicate that it is the instrument of choice to fill a gap that exists in nuclear instrumentation between the conventional methods of uptake measurements and scanning and the whole-body counters. However, conclusions on its quantitative properties have to be made cautiously, because the evidence on the basis of which these properties have been discussed is too little. But there are indications that this might be largely a matter of learning how to do it, and of refining the techniques. Studies at tracer levels have been disappointing, but the results with therapeutic doses, including pure beta emitters, were encouraging, and even suggest that the instruments may bring us closer to a solution of the problem of dosimetry of internal radiation.

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The Research Branch, Division of Radiological Health, United States Public Health Service is sponsoring a symposium entitled, "Technological Needs for Reduction of Patient Exposure from Diagnostic Radiology." The purpose of this meeting is to evaluate the status of laboratory research as it applies to this subject. Approximately fifteen papers will be given which will summarize the state of the art and point out future areas for investigation. The four main categories which will be covered are human and phantom dosimeters, radiographic equipment, fluoroscopic and intensifier equipment, and radiographic grids, screens, and films. Drs. H. Wyckoff, C. Braestrup, R. H. Morgan, and E. W. Webster will act as moderators for these sessions.

The dates of this meeting are March 5 and 6, 1962. The place is the main auditorium of the Health, Education, and Welfare Building, Washington, D. C. For information and tickets contact:

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JOURNAL OF NUCLEAR MEDICINE 3:41, 1962

A Simple Measure of Thyro-Binding by Plasma: A Test of Thyroid Function[1]

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INTRODUCTION

In 1957 Hamolsky described the "*in vitro* red blood cell uptake of I^{131} labeled l-triiodothyronine" (RBC-T3 uptake) as a measure of thyroid function (1). He found that l-triiodothyronine (T3) added to the whole blood was distributed between the red cells and the plasma, and that the distribution was dependent upon some not yet well-defined property of the plasma (2). This property, which we have termed "thyro-binding power", is perhaps in turn dependent upon the thyroxin-binding protein and the degree of its saturation by thyroxin; at least this explanation fits the important clinical finding that the amount of T3 going on to the red cells is increased in hyperthyroidism and decreased in hypothyroidism and pregnancy. Although the determinants of the test are not well understood, the RBC-T3 uptake has become a useful and widely used clinical test (3,4,5).

In our experience, most of the difficulties with the RBC-T3 uptake relate to the use of live red cells. Some of these difficulties are common to any use of blood cells and include problems of storage, anticoagulation, hemolysis, careful handling, and washing. More specifically, the number of washes done as part of the procedure has been found to affect the result of the RBC-T3 uptake (6), and the total elapsed time required for washing has affected the result in our laboratory. More difficult to control is the hematocrit which in spite of the correction made for it as part of the RBC-T3 uptake has been found to affect the result (7). To avoid the use of red blood cells, an ion exchange resin known to compete with the plasma for the T3 has been used to replace the red blood cells in tests otherwise comparable to the RBC-T3 uptake. The method has worked well as a thyroid function test (8), and with the use of different resins the method has been extended to the identification of the particular binding protein involved in the phenomena (9).

In our laboratory the method was further modified in an attempt to maintain the advantages of the Hamolsky and later procedures, to increase their reliability, and to simplify the procedures. We believe our method is the simplest described to date, and in over 500 tests it has given good clinical results.

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1. From the Palo Alto Medical Clinic, Palo Alto, Calif.

METHOD

In outline, this test consists of the labeling of a resin by I^{131} labeled 1-triiodothyronine, the incubation of plasma to be tested with small portions of this labeled resin, and a determination of the amount of label leaving the resin to go into the plasma.

Preparation of the "labeled" resin:

In a 25 ml. flask place:

(1) 15 ml distilled H_2O.
(2) 2.5 micrograms of I^{131} labeled 1-triiodothyronine.
(3) 5 grams (dry weight) of a strongly basic anion exchange resin (IRA 400)[1], chloride form.

This mixture is shaken at 37°C for 30 minutes. At the end of this time the resin is filtered, washed once with distilled water, and allowed to dry at room temperature.

Approximately 0.1 gram portions of this labeled resin are placed in individual glass test tubes (100 × 16 mm), counted in a standard scintillation well counter, and the activity on the resin is determined in microcuries. Any tube in which the activity varies from the mean by more than 10 per cent is discarded.

The assayed tubes are then kept at room temperature until used, but for no longer than 2 weeks.

Determination of Plasma Thyro-Binding:

Procedure

(1) 2 ml of plasma to be tested are added to each tube. (EDTA or a double oxalate, but not heparin, may be used as anticoagulant.)

(2) The tubes are shaken at 37°C for 2 hours; at the end of that time the resin either is allowed to settle to the bottom of the tube or is spun down.

(3) 1 ml of plasma is removed, and its activity in microcuries is determined in a scintillation well counter.

Calculations:

The per cent of the total activity in the plasma is determined:

$$\frac{2 \times \text{microcuries in 1 ml of plasma} \times 100}{\text{total microcuries in tube (corrected for decay)}} = \% \text{ "thyro-binding" by plasma.}$$

RESULTS

In euthyroid individuals, the average per cent of thyro-binding by the plasma has been about 11. The average deviation from the mean of samples done in

1. Mallinkrodt Chemical Co., St. Louis.

replicate on any one run has been 1.9 per cent. However, the deviation of samples of the same plasma run at different times has been much greater. Some of this variation has been due to inadequate control of such things as temperature, length of time of incubation, time between the end of incubation and removal of plasma from the tubes, density of the label on the resin, and the amount of resin in the tubes from one time to another. More careful control would eliminate some of the variations due to these factors but there are undoubtedly other unrecognized contributing problems.

Because of this variation and to normalize the results, the per cent of thyro-binding in each test is compared to that of a standard plasma. The pooled standard plasma is kept frozen until used. With each test run, the per cent of thyro-binding of this standard plasma is determined in triplicate, and the per cent of thyro-binding of each test sample is divided by their mean. The results of each test are expressed as a "thyro-binding index" in which the value of the standard pooled plasma is unity. Thus plasma with high binding power has a high index, and that with low binding power a low index.

To determine whether the method gave reproducible results, 20 single determinations were made on the same plasma over a period of time which required the use of three different batches of labeled resin. Standard statistical methods were applied with the following result: Mean = 1.12, Standard deviation = .049.

AN EVALUATION OF THE METHOD AS A TEST OF THYROID FUNCTION

The thyro-binding index has been determined on over 500 samples of blood submitted to our laboratory for the RBC-T3 uptake test. The test was requested by physicians of the Palo Alto Medical Clinic as a diagnostic procedure, or as an aid in their evaluation of patients with known thyroid disease. A comparison of the RBC-T3 uptake with the thyro-binding index showed a fair inverse correlation.

The results of the test were compared to the clinical findings in 501 patients. Each patient was placed in one of three groups depending upon his thyroid status as determined by a review of the clinical record or by the physician's diagnosis.

(1) *Hyperthyroid group:* This includes 30 individuals who were diagnosed as hyperthyroid on some basis other than the RBC-T3 uptake or the thyro-binding index. The group includes two individuals who were in the hyperthyroid stage of acute thyroiditis, four who were thyrotoxic secondary to oral ingestion of dessicated thyroid, and several who had been very recently treated for hyperthyroidism but who were still clinically thyrotoxic.

(2) *Hypothyroid or pregnant group:* This includes 47 patients. They were diagnosed as hypothyroid on the basis of clinical findings or tests other than the thyro-binding index or the RBC-T3 uptake. So-called "hypometabolic" patients were not included, nor were hypothyroid patients on adequate replacement therapy. Pregnant pateints were included since they are indistinguishable from this group on the basis of this or the RBC-T3 uptake test.

(3) *Euthyroid group:* This includes all patients not in either of the other groups. The group cannot be called normal since it includes patients with a wide variety of illnesses or abnormalities. Some of the latter include factors known to affect the RBC-T3 uptake, and presumably the thyro-binding index as well.

The result obtained on 501 patients appear to be normally distributed (Fig. 1). The mean and standard deviation of the results in each group are:

Euthyroid:	Mean = 1.010,	S.D. = .097
Hyperthyroid:	Mean = .785,	S.D. = .028
Hypothyroid or pregnant:	Mean = 1.301,	S.D. = .091

As in any test, the overlap of values between diagnostic groups is undesirable although usually physiological. The overlapping shown in Figure 1 would be reduced by eliminating from the euthyroid group those individuals possibly affected by estrogen administration (which may raise the thyro-binding index), or by protein abnormalities, bishydroxycoumarin, liver disease, etc. (which may lower the thyro-binding index). Additional overlapping would have been elimi-

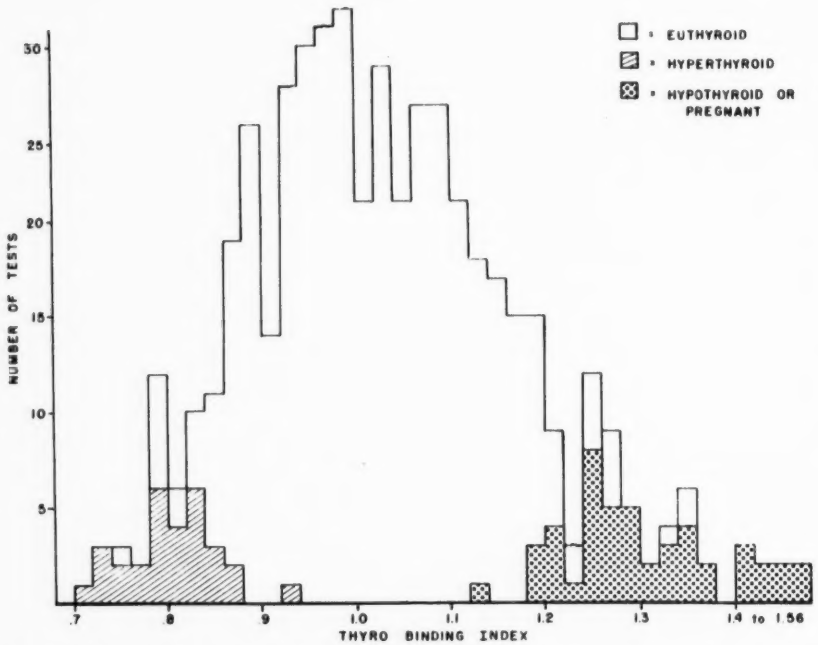

Fig. 1. The results of the thyro-binding index in 501 single determinations: Those individuals determined to be hyperthyroid and hypothyroid or pregnant on the basis of other tests and clinical information are indicated. The remainder, while euthyroid, is not a *normal* group since it includes patients with a variety of abnormalities as seen in a general medical practice.

nated if the tests had been done in duplicate. Nevertheless, the results permit an arbitry grouping of the test values as seen in Table 1. These range of values show a diagnostic specificity which is nearly that of other measures of thyroid function (10).

No comparison of the results of the PBI or the in vivo thyroidal I^{131} uptake with the thyro-binding index has been made. However, these were the major criteria upon which the diagnosis of either hyperthyroidism or hypothyroidism were made.

DISCUSSION

The test has been set up with some specifications established on either a practical or empirical basis, but certain variables have been considered.

The amount of labeled resin used in the test affects the thyro-binding by the plasma. When the amount of T3 on the resin is constant, the use of increasing amounts of labeled resin is associated with a decrease in the percentage of thyro-binding by the plasma, a decrease in the sensitivity to small differences in the amount of resin, and an increase in the differentiation between plasmas of different thyro-binding capacity. All tubes were checked and found to contain 0.040 to 0.060 μgm of T3. This variation was due both to differences in density of the label and to approximations in the measurement of the resin, but within this tolerance neither significantly affects the results of the test. The amount of T3 in the plasma is approximately 0.0025 microgram/ml, a concentration similar to that used in the RBC-T3 uptake (2).

The effect of the resin and storage on the triiodothyronine has been checked by chromatographic studies of the radioactive material in the plasma following the test and by doing the test with samples of resin kept dry at room temperature for periods up to 88 days. The former studies identified the activity in the plasma as 1-triiodothyronine-I^{131}. With storage of the labeled resin a decrease of about 10 per cent in the apparent thyro-binding appeared over a two week period. Presumably this was due to some breakdown of T3 with the released iodine remaining on the resin. On storage for longer periods of time there was a gradual increase in the thyro-binding by plasma, presumably due to weakening of the resin bond.

A study of the effect of time and temperature has shown that the T3 in the plasma reaches a constant value at about one hour at 37°C, in about two hours at room temperature. At two hours small variations in either time or temperature do not significantly affect the result.

TABLE 1. THYRO-BINDING INDEX OF PLASMA

	Hyperthyroid	*Euthyroid*		*Hypothyroid or pregnant*
Range of value	< .86	.86 to 1.20		> 1.20
% of patients outside of range	10%	5% below	5% above	10%

The use of serum in the test has been compared to that of plasma. The thyro-binding of a serum has consistently been less than that of its plasma but the relationship between the two has not been constant. The source of this difference has not been identified, but the addition of anticoagulants to serum has no effect on thyro-binding.

The use of l-thyroxin (T4) would have an advantage over that of l-triiodothyronine because of its greater stability (11). For this reason the test has been done using T4 as well as T3 and the results compared. The thyro-binding of T4 by plasma at two hours has been less than that of T3, a finding in disagreement with observations made by other methods and at different time intervals (11). The results with T3 and T4 were otherwise comparable, and a good correlation was shown between the thyro-binding indices determined by the two tests on different samples of plasma.

SUMMARY

The use of a resin previously labeled with l-triiodothyronine-I^{131} makes possible a very simple qualitative measurement of the thyro-binding power of plasma. In clinical use this has been a satisfactory measure of thyroid function. With this simplification, and particularly with the commercial preparation of labeled resin, an easily and quickly done in vitro test of thyroid function is available to any laboratory possessing satisfactory I^{131} counting equipment.

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JOURNAL OF NUCLEAR MEDICINE 3:47, 1962

Experimental Studies for Scintillation Scanning of the Pancreas[1,2,3]

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INTRODUCTION

Since the pancreas has not been visualized radiographically without operative procedures, scintillation scanning should be studied as a method of mapping this major organ. Our initial efforts on the development of isotopic tracers to make scanning of the gland possible have given a moderate differential concentration in the pancreas and are reported briefly here.

Radioiodinated derivatives of organic acids and radiozinc chelates of amino acids have been studied in particular. The radioiodinated compounds were uniformly unsatisfactory because of high concentrations in the stomach and low values in the pancreas. Radiozinc chelates with glycine and arginine showed the greatest promise of the amino acid complexes. Their differential uptake by the pancreas was increased by the administration of other, stable, zinc salts, presumably by increasing the zinc content of the liver so that more radiozinc was eliminated by way of the pancreas.

METHOD

Male, Sprague-Dawley rats, weighing 400-425 grams, and fasted 18 hours prior to injection, were used for screening experiments. The radiozinc chelates were prepared by adding 10 ml of a normal saline solution of $Zn^{65}Cl_2$, containing approximately 1μc/ml, to 10 mg portions, respectively, of each of the 20 natural amino acids, or amino acid hydrochlorides. By the addition of 10 mg of anhydrous sodium acetate the reaction of the solutions was adjusted to, or near, pH 4. Control solutions were prepared by adding only the 10 mg of anhydrous sodium acetate to 10 ml of the $Zn^{65}Cl_2$ solution, thus forming $Zn^{65}(OAc)_2$. The tracers were given intravenously by tail vein, and the rats killed by exsanguination 1-8 hours later. The pancreas, liver, stomach, kidney, and spleen were dissected free of fat, and the activities per gram determined in a well counter.

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2. This work was supported in part by Grant C-3952, Research Grants Division, National Institutes of Health, U. S. Public Health Service.

3. Presented at the Seventh Annual Meeting of the Society of Nuclear Medicine, June 22-25, 1960, Estes Park, Colo.

4. Advanced Clinical Fellow in Radiation Therapy, American Cancer Society.

RESULTS

The highest concentration of activity in the pancreas after administration of an amino acid chelate alone was obtained with glycine zinc. The concentration of radiozinc in the pancreas was further enhanced by simultaneous injection of stable zinc gluconate, and slightly increased by stable zinc acetate. The data given in Table 1 are expressed as pancreas to liver ratios, P/L, obtained by dividing the cpm/gm of the pancreas by the count of the liver. Ratios for other competing organs are not given since in no case was the radioactivity of the other organs sufficiently high to interfere with the pancreas.

The highest P/L ratio obtained was 3.6, and this resulted 3 hours after 5 mg of zinc gluconate was given simultaneously with the glycine radiozinc. Injection of the same mixture to fed rats resulted in a P/L ratio of 3.2 at 2 hours. The highest ratio of the control radiozinc acetate was 1.1 at 1 hour.

DISCUSSION

An understanding of the clearance of zinc is essential for devising methods of increasing the uptake of radiozinc by the pancreas. Unfortunately, little clearance data are now available for the development of working hypotheses. In the single publication relating to zinc clearance, Gilbert and Taylor (4) imply that glycine zinc is cleared very rapidly from the blood but give neither specific pathways nor rates. To measure the overall physiological rate of clearance, stable serum protein zinc was exchanged with radiozinc in vitro by these authors, the product reinjected into rats, and in 30 minutes 95 per cent of the radiozinc was cleared from the blood.

TABLE 1. RATIO OF PANCREAS/LIVER (P/L) CONCENTRATIONS OF ZINC—65 GIVEN INTRAVENOUSLY UNDER VARIOUS CONDITIONS TO FASTED ADULT MALE RATS.

Tracer	*Added Zinc Gluconate (mg)*	*Hours after Injection*			
		1	*2*	*3*	*4*
Zinc—65 Acetate	0	1.1	0.7	—	—
Zinc—65 Acetate	2.5	1.4	2.5	1.5	—
Zinc—65 Acetate	5.0	—	1.8	2.2	2.8
Glycine Zinc—65	0	0.8	1.2	2.0	2.1
Glycine Zinc—65	5	—	2.8	3.6	1.6
Glycine Zinc—65	5 (fed)	—	3.2	1.9	1.9

Zinc is excreted from the body largely by way of the gastrointestinal tract. Although 10-20 per cent of zinc may be eliminated through the skin and hair, urinary and biliary excretions are very low. Experimental studies on the amounts excreted in the gastrointestinal tract, largely by way of the pancreas, vary widely. In zinc-65 studies, Sheline, Chaikoff et al. (6) found 50 per cent eliminated in 7 days in mice, and 23 per cent in 15 days in dogs. Gilbert and Taylor (4) determined with rats that 50 per cent of injected radiozinc was eliminated in 7 days by way of the gastrointestinal tract. As was shown by Birnstingl (3), injected zinc-65 appeared in pancreatic juice as early as 15 minutes after intravenous administration, and reached peak levels at 3-6 hours in dogs. The comprehensive studies of the metabolism of zinc-65 in rats by Ballou (1) show that the activity of the pancreas is moderately higher than liver, spleen and kidney three hours after intravenous injection under ether anesthesia.

The role of the liver is of key importance in zinc distribution. A variable but large portion of administered radiozinc in rats is taken up by the liver, and this is redistributed over a period of days with slow, steady incorporation in bones, skin, hair, and muscle (2). The reported values for the uptake by the liver vary. Thus, Meschan (5) found 85-88 per cent of injected zinc-65 in dog liver 2 hours after administration, and Sheline, Chaikoff et al., (7) reported 38 per cent at 3 hours. Since the liver is anatomically superimposed over the head of the pancreas, the high liver uptake of radiozinc creates an obstacle to effective scanning of the pancreas. Prevention of high level tracer zinc deposition in the liver is essential if the pancreas is to be scanned and this has been achieved in this study by simultaneously injecting stable zinc gluconate. With effective blockade of the binding sites of zinc in the liver, the level of radiozinc in the pancreas was increased markedly from a P/L ratio of 2.1 to 3.6. This approach offers promise for successful pancreatic scanning, but it will be necessary to increase the P/L ratio to 6 or more before clinical scanning can be considered.

SUMMARY

Radiozinc chelates with each of the naturally occurring amino acids have been examined as tracers for scintillation scanning of the pancreas. The studies have been made by tissue counts following intravenous administration of the chelates to fasted, male, adult rats. Glycine radiozinc accumulates most successfully in the pancreas to give radiozinc concentrations twice those found in the liver. Simultaneous administration of stable zinc gluconate with the glycine radiozinc increases the pancreas concentration to 3.6 times that of the liver.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the March, 1962 issue must be in the hands of the Editor before February 1, 1962.

JOURNAL OF NUCLEAR MEDICINE 3:51, 1962

The Use of a Photocopying Process for Erasing the Background of Photoscans and Accentuating Small Differences in Optical Density[1]

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INTRODUCTION

A reliable method has been found by which the presentation of information on copies of photoscans* can be varied to make small differences in density on the photoscan readily discernable. The method depends upon a cut-off characteristic of the copying paper which produces no marking if a certain total quantity of light has reached the paper. Thus, by varying the time of illumination the threshold density for copying from the photoscan negative can be varied at will. From a series of copies at different total illumination a clarified localization of areas of greater radioactivity appears.

Other techniques available include electronic circuits for background cut-off (1, 2, and 3) and closed circuit television (4) all of which eliminate certain optical densities on a photoscan. These methods are rather involved and expensive, and permanent records are not always available without additional equipment.

In the method presented here, a photocopy printer was used to reproduce photoscans. A photoscan calibration film was used to determine the length of exposure time necessary to erase all information less than a particular optical density. With this method a series of reproductions can be made, eliminating different optical densities, and the series is available for permanent records. An example will be shown which illustrates how a small radioactive target can be located inside a larger region containing a lower concentration of radioactivity.

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*A photoscan consists of a pattern on film representing the distribution of radioactivity in an object. As the amount of radioactivity increases the optical density on the film increases.

MATERIALS AND METHODS

Commercial photocopy equipment with Agfa and two other brands of papers and solutions were used. The negative papers are sensitized with orthochromatic emulsions and available in three speeds, type CpG a slow speed, type CpM a moderate speed, and type CpN a fast speed.

Calibration films and photoscans were made on Blue-Brand X-Ray film (Kodak) with a commercial scintiscanner* having a modified photoscanner attachment. The photoscanner has a modulated neon light which glows continuously and increases in intensity as the counting rate increases. The photoscanner also has contrast and background cut-off controls. For the calibration film the light source was set at different intensities, and lines with different optical densities were obtained. Optical density was determined with a MacBeth-Ansco Densitometer.

The photocopy printer consists of a light source with twelve 40 watt light bulbs, a yellow filter placed above the light source, and a timer. The timer was checked for accuracy so that exposure times could be reproduced with a high degree of reliability.

The copying process consists of placing the photoscan on top of the yellow filter on the printer and then placing the negative paper, emulsion side down, on top of the photoscan. The negative is exposed for various lengths of time as the light passes through the photoscan. Development of the film and printing of the positive is a "one step" process. The exposed negative and a positive paper are placed with emulsion sides together in the developing solution and are passed through rollers which remove the excess solution. They are left in contact for 10 to 30 seconds and then separated. The entire process requires from one to five minutes, depending on the type of negative used and the optical density to be erased.

No dark room is required for this process, although the lighting conditions of the area should be controlled. Light intensity in the room was measured with a Brockway Model S photographic exposure meter which was calibrated in foot-candles.

RESULTS

1. *Calibrating the Photocopy Process*

One of the calibration films used to calibrate the photocopy equipment and a photocopy reproduction of it are shown in Figure 1. On the film the optical

*A 2-inch NaI crystal and either a 7-hole or a 19-hole focusing collimator were used. The resolution as determined at 8.0 cm from the face of the collimator with a point source was 0.90 cm for the 7-hole collimator and 0.50 cm for the 19-hole collimator. The pulses from the photomultiplier tube are fed through a spectrometer, set on the iodine photopeak of 367 kev, to a scaler. Depending on the scaling factor every 1, 2, or 4 pulses are fed to the integrating circuit in the photoscanner. Recently, the neon light in the photoscanner was replaced with a Sylvania 48-D tungsten light bulb, which provides a nearly linear response of optical density versus counting rate.

densities varied from 0.18 at the bottom to 1.35 at the top. In the photocopy reproduction made with an exposure of 60 seconds (CpG paper) only optical densities greater than 0.74 were reproduced. The ability of the photocopy process to differentiate between two slightly different optical densities is illustrated by the 0.74 and 0.80 lines; although these lines can not be distinguished visually from one another on the calibration film, they can be distinguished from one another very readily on the photocopy reproduction.

A second calibration film (not shown) was made where the different optical densities were in different areas on the film. The optical density erased did not vary from one position on the printer platform to another, which illustrated that the light illuminates the printer platform uniformly.

Photocopy reproductions of the calibration films were also made with a wide range of exposure times and with different types of Agfa paper. The optical density erased varies linearly with the logarithm of the exposure time (Fig. 2), and the type of paper to use depends on the optical density to be erased.

To test the reproducibility of the method, four different batches of positive paper and four batches of negative paper of type CpG were used with developing solutions of various ages, i.e., freshly prepared, 1 day after preparation, 3 days after preparation, and a solution which had been used for 7 days to develop

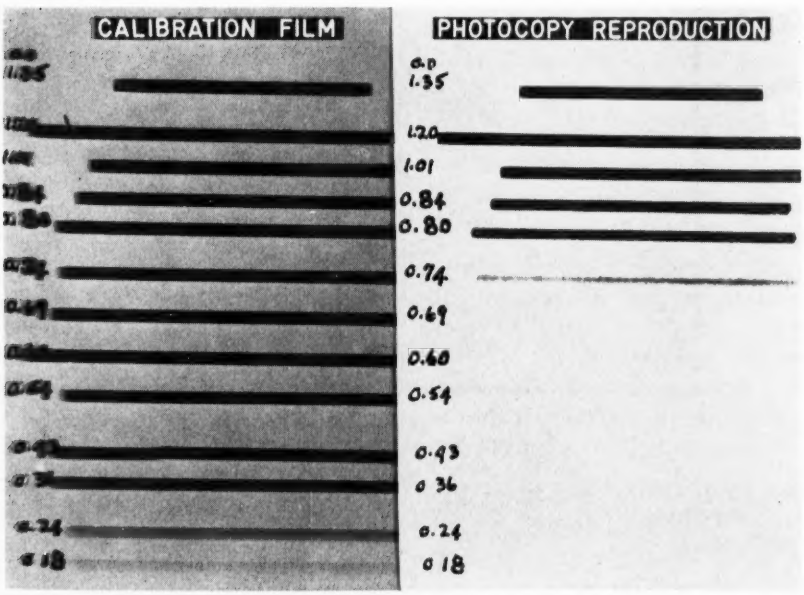

Fig. 1. Calibration film with a photocopy reproduction of it (60 second exposure of CpG paper)

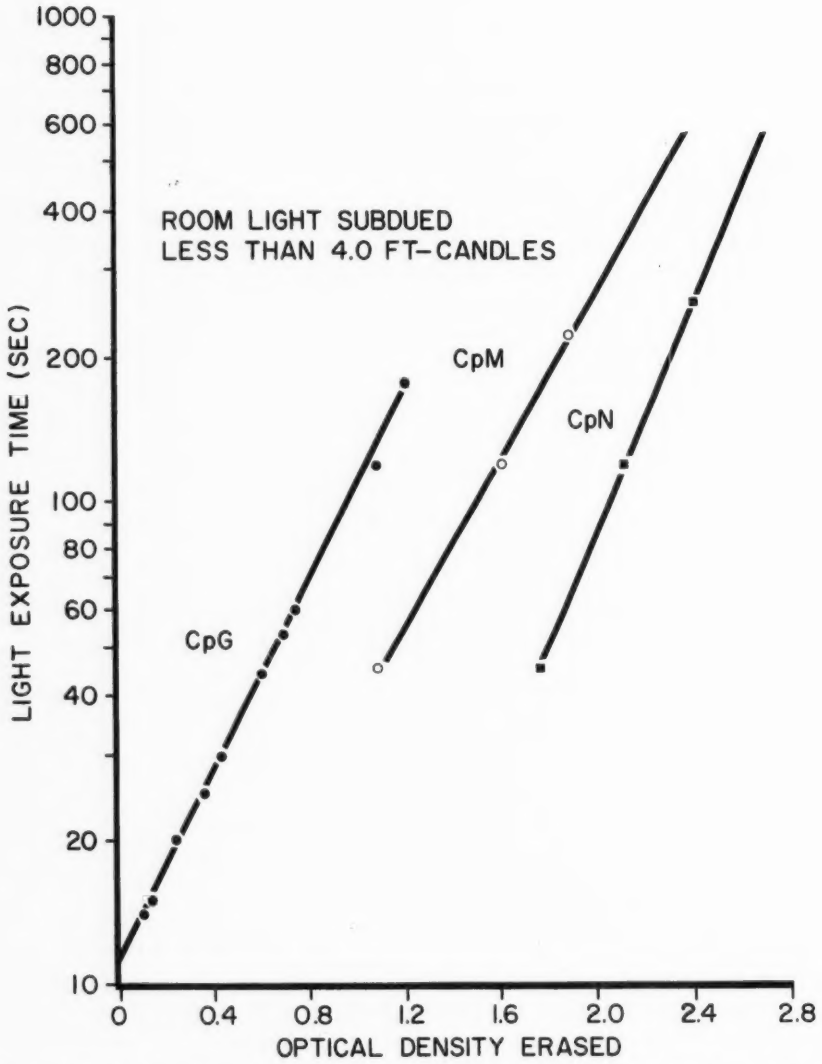

Fig. 2. Optical density erased versus time of exposure of negative to light for three types of Agfa Paper.

approximately 400 copies. Excellent consistency was found between the different papers and developing solutions.*

Two other commercial brands of photocopy paper and developing solution which were tested for reproducibility were found to be unsatisfactory. This contrasts with excellent results obtained with Agfa paper as shown in Figure 2.

The effect of light intensity in the room where the photocopy equipment is used was studied. Varying the room lighting from 4 to 32 foot-candles had a marked effect on the moderate speed CpM paper and a lesser effect on the slow speed CpG paper. Thus, when using the paper for accurately calibrated reproductions, it is necessary to keep the lighting in the room constant and preferably as low as practicable.

2. *Photocopy Reproductions of Brain Scans*

To illustrate how this technique can be used practically, two brain scans of the same patient with photocopy reproductions are shown in Figure 3. At the top, the original photoscans are shown. The photoscan on the left was obtained with a considerable amount of the background erased electronically, and the photoscan on the right was obtained with very little background erased. The photocopies appearing below the photoscans were made with different optical density cut-offs as indicated by the numbers on each copy. The optical densities erased were determined from the exposure times and the calibration curves in Figure 2. Note that the 0.58 reproduction of the photoscan on the right is similar to the original photoscan on the left, and that the 0.7 reproduction is similar to the 0.2 reproduction. This indicates that the same end result can be obtained by erasing the background either electronically or with the photocopy process.**

3. *Calibrating the Photocopy Process in Terms of Counting Rate*

It is possible to specify the counting rates which are eliminated in each photocopy reproduction by relating the optical density on the photoscan to the counting rate. This relationship was obtained experimentally by scanning at a given speed while pulses were fed into the photoscanner at different rates. An example of such a calibration for different photoscan settings is shown in Figure 4. For a given scanning speed the slope of the curves can be altered by changing the light aperture size on the photoscanner. Curves were also obtained for different scanning speeds. The shape of the curves is dependent on the light out-put from the bulb and the logarithmic response of the x-ray film. By developing the

*After the developing solution was used for approximately a week the copies were slightly discolored. This can be avoided by washing the copies with running water for five minutes and then drying them.

**This patient had a tumor in the left parietal lobe as diagnosed by the electroencephalograph. The dark area in the upper part of the scan, however, is also characteristically found in normal patients and is probably caused by RISA in the superior sagittal sinus.

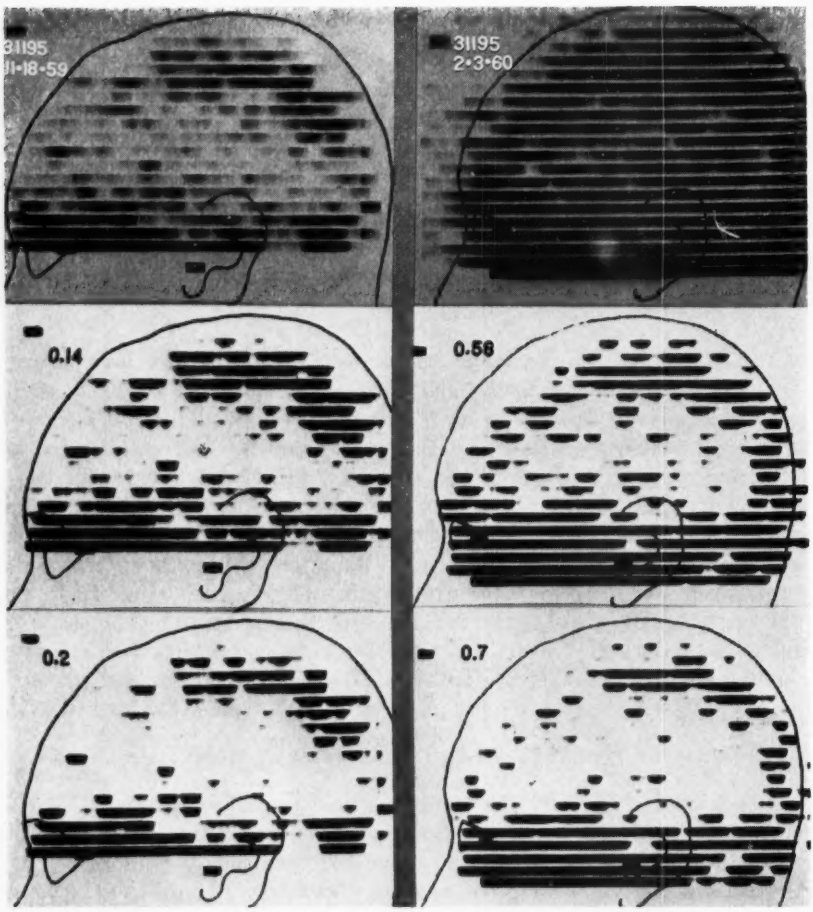

Fig. 3. Two brain scans of the same patient with photocopy reproductions. The patient was given 500 microcuries of RISA and scanned 24 hours later. (A speed of 1.5 mm/sec was used) The brain scan at the upper left was obtained with a considerable amount of background erased electronically, and the brain scan at the upper right was obtained with little background erased. The photocopies are shown below the brain scans with the optical densities which were erased.

photoscan under controlled conditions of time and temperature these curves are reproducible.

4. *Using the Photocopy Process to Illustrate a Radioactive Target Positioned Within a Region Containing a Lower Concentration of Radioactivity.*

A 12-cm cube was filled with 17.8 microcuries of I-131 giving a concentration of 0.0103 μc/ml. A small 2-cm cube was filled with 0.411 microcuries of I-131 giving a concentration of 0.0514 μc/ml, five times higher than that in the large cube. The small cube was positioned with its center 6 cm from the bottom of the large cube and 1.4 cm from the center of one side. A photograph of the two cubes is shown in Figure 5. The cubes were scanned* with the face of the 7-hole collimator 2 cm above the large cube. When the collimator was positioned directly over the center of the large cube, a counting rate of 815 cpm was obtained. Over the center of the small target a counting rate of 992 cpm was obtained. This is a target to non-target counting ratio of only 1.22. This change in counting rate is

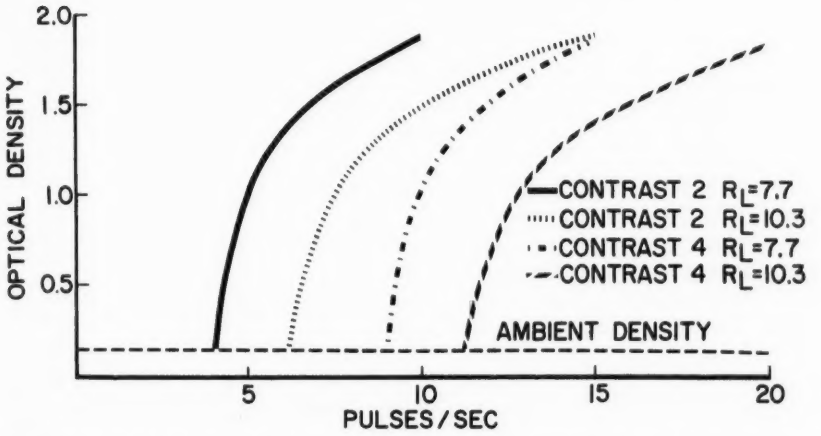

Fig. 4. Optical density on photoscan versus pulses per second input. A family of curves was obtained for different settings of the photoscanner. Only curves for settings of contrasts 2 and 4 and R_L of 7.7 and 10.3 are shown. The scanning speed was 1.25 mm/sec and the light aperture size was 1.5 mm. For a given scanning speed the slope is altered by changing the light aperture size. Curves were also obtained for different scanning speeds.

*Scanning conditions were as follows: scanning speed 1.25 mm/sec, contrast 4, $R_L = 10.3$, scaling factor = 1, integrating time constant = 4 sec, and compensation for memory lag = 8 mm. The memory lag existing in the integrating circuit of the photoscanner causes the information obtained while scanning in one direction to be displaced relative to the information obtained while scanning in the opposite direction. This is compensated for by automatically changing the length of the rod connecting the scintillation probe and the photoscan light source each time the scanning direction is reversed.

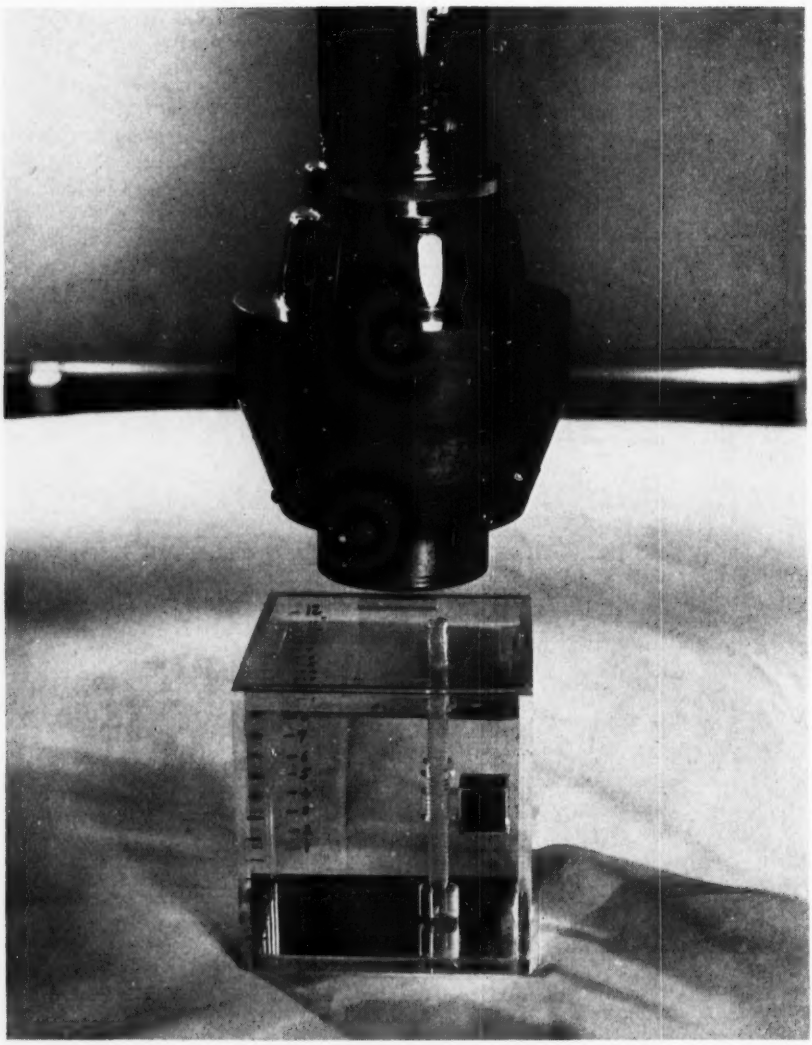

Fig. 5. Picture of cube phantom placed under the scintillation probe. The small 2-cm cube near the edge of the larger 12-cm cube contained I-131 at a concentration of 0.051 μc/ml, five times higher than that in the larger cube (See text for details).

only 2.2 times larger than the per cent standard deviation in the counting rate.** Thus, it was necessary to differentiate the change in counting rate as the collimator passed over the target, from the statistical fluctuations.

The photoscan with three photocopy reproductions are shown in Figure 6. It is difficult to distinguish the target region from the statistical fluctuations over the non-target region. However, in the photocopy reproductions the target is more easily visualized. With the use of Figures 2 and 4 the optical densities and count-

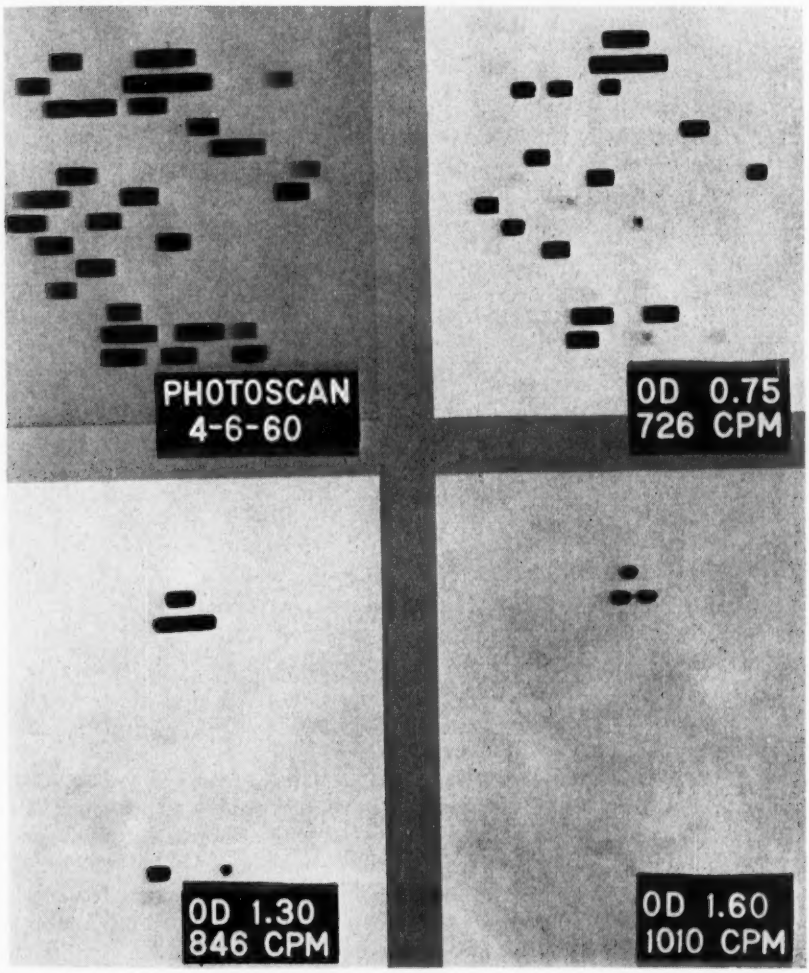

Fig. 6. Photoscan of cube phantom with photocopy reproductions. The optical densities and counting rates erased are indicated on each photocopy.

**Per cent standard deviation $= 100/\sqrt{2\ (\text{counting rate})\ (\text{time constant})}$. Preliminary studies indicate that the per cent change in counting rate should be 2-3 times larger than the per cent standard deviation in order to detect a target with a high degree of reliability.

ing rates erased are indicated on each photocopy reproduction. Note that when only counting rates greater than 1010 cpm are reproduced, all of the non-target area has been erased and only the target area remains. This agrees very well with the actual counting rates found, 992 cpm over the target region and 815 cpm over the non-target region.

Thus, with the photocopy process it was possible to accentuate the difference between a target and non-target region represented on a photoscan. Furthermore, it was possible to quantitate the difference.

5. *Photocopy Reproductions of a Mock-thyroid Scan*

A thyroid phantom made of lucite was filled with 27 ml of an I-131 solution having a concentration of 0.5 μc/ml. A small 1-cm^3 rubber stopper was placed near the edge of one lobe. The phantom was scanned* with the face of the 19-hole collimator 8.0 cm above the center of the phantom.

The counting rate (1100 cpm) when the collimator was positioned over the rubber stopper was 12 per cent lower than the counting rate (1230 cpm) when the collimator was positioned over the corresponding part of the opposite lobe. This change in counting rate is approximately equal to the per cent standard deviation (11%).

The scintigram and photoscan with photocopy reproductions are shown in Figure 7. The optical densities erased with the corresponding counting rates are indicated on each photocopy. Although neither the scintigram nor the photoscan show the small void, the photocopy reproductions demonstrate an area of lesser radioactivity near the edge of the lobe on the right.

DISCUSSION

By comparing original photoscans and photocopy reproductions of them, it is apparent that the same end result can be achieved with either the photocopy equipment or the electronic background cut-off system. There are, however, several advantages to the photocopy method.

1. The original photoscan can be obtained without any background erase and loss of information.

2. Optical densities on a film which do not differ enough to be differentiated visually can be distinguished one from the other very readily on a photocopy reproduction of the film. Differences of only 0.05 optical density units can be visualized (Fig. 1).

3. The optical densities to be erased from the original scan can be precisely specified. When the optical density is calibrated in terms of counting rate, the background cut-off can also be specified in terms of counting rate. From Figure 4, it can be seen that differences of only 3 per cent in counting rate can be visualized (corresponding to a 0.05 optical density difference).

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*Scanning conditions were as follows: scanning speed 2.0 mm/sec, contrast 2, $R_L = 7.0$, scaling factor = 4, integrating time constant = 2 sec, and compensation for memory lag = 5 mm.

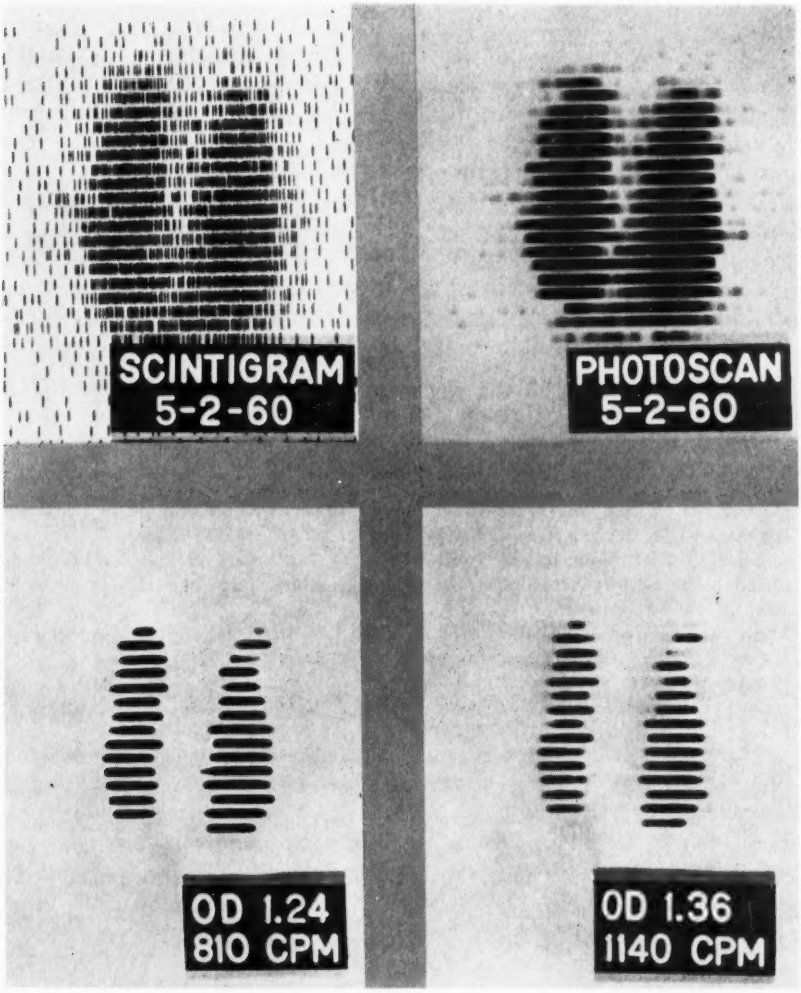

Fig. 7. Scintigram and photoscan of mock-thyroid which contained 0.5 μc/ml of I-131 and a 1-cm³ void near the edge of the lobe on the right. Photocopies of the photoscan are shown, and the optical densities and counting rates erased are indicated on each photocopy.

4. A permanent record consisting of a series of reproductions with different background cut-offs can be obtained. Such a series can be of great value to the clinician making his diagnosis.

5. Less than fifteen minutes are required for a complete series of reproductions.

6. The photocopy equipment is relatively inexpensive, costing less than four hundred dollars, and copies can be made for approximately six cents each.

SUMMARY

Photoscans which represent the distribution of radioisotopes by variations in optical density can, by a controlled photocopying process, be made to accentuate small differences in the distribution of radioisotopes. Optical densities less than a specified amount can be eliminated, and optical densities on the photoscan which do not differ enough in order to be differentiated visually can be reproduced such that they differ greatly in density. The optical densities which are erased from a photoscan can be accurately determined by calibrating in terms of exposure time of the photocopy negative. By calibrating the optical density of the photoscan in terms of counting rate it is also possible to specify accurately the counting rates which have been eliminated. Examples of using this technique on a brain scan, mock-thyroid scan, and on a scan of a phantom are shown.

This work was carried out in part with the assistance of American Cancer Society Grant No. IN-43-A-12.

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JOURNAL OF NUCLEAR MEDICINE 3:63, 1962

The Inadequacy of Radio-Iodinated (I^{131}) Iodipamide As A Liver Function Test[1,2]

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INTRODUCTION

Radio-iodinated (I^{131}) Iodipamide Sodium Solution has been reported of value as a liver function test. Work done in the dog by McLaren, et al. (1) indicated that there was a correlation between the clearance of radioactive iodipamide solution from the blood and its excretion in the urine with hepatic disease and biliary obstruction. In human beings McLaren, et al. (2) found that the clearance of radioactivity from the blood and excretion of radioactivity into the urine of patients with liver disease differed significantly from similar determinations in controls. We have attempted to further test the use of radioiodinated iodipamide solution in differentiating between patients without liver disease, those with obstructive biliary disease and those with hepato-cellular disease.

PROCEDURE

On the day before examination the thyroid gland was blocked by the administration of Lugol's Solution. On the day of examination with an empty urinary bladder, 0.5 microcurie of labeled iodipamide sodium solution (Cholografin®) per kilogram was injected intravenously. Blood and urine samples were taken at 5 minutes, 2, 4, 6, 12 and 24 hours. The 5 minute sample was accepted to represent complete mixing in the blood stream and was charted as 100 per cent. Two ml of each sample was counted in a well scintillation counter and compared with the initial dose and expressed as a percentage of the initial dose.

1. Research performed in the Isotope Division of the Department of Radiology, Albert Einstein Medical Center, Research # N-74.
2. Radio-iodinated (I^{131}) Iodipamide was supplied by Dr. Paul Numerof, The Squibb Institute for Medical Research, New Brunswick, New Jersey.

Each urine sample was counted separately and the counts recorded as percentage of total dose used in the test. As the result, the percentage values in data obtained on the urines are cumulative until the 24 hour level. The figure pertaining to the blood radioactivity represents the actual percentage of radioactivity in the blood at the time of collection.

RESULTS

A group of 32 hospitalized patients was examined. The cases were divided into 18 patients who had no hepatic disease, 8 patients with hepato-cellular disease and 6 patients with obstructive biliary disease (Table 1). There was no significant difference between the three rates of fall of dye concentration in blood. The blood level dropped in each group, on an average of 4 per cent each hour. In other words, whatever the blood level was at any one time, approximately 96 per cent would be expected to be found one hour later. This finding implies that the clearance of radioactive Cholografin® from the blood in normal individuals and in patients with liver disease is not a discriminating function of the liver.

Fifty per cent of the radioactive Cholografin® was removed from the blood in hospitalized patients without hepatic disease in 4.8 hours. In patients with hepato-cellular disease the approximate time for removal of 50 per cent was 6.8 hours and in patients with hepatic obstructive disease the time was 6.0 hours. These findings are in contrast to the reports of other investigators (1) (2) who found a significant difference in the time needed for radioactivity in the blood to be reduced to one-half the value obtained immediately following an injection.

Table 1.

Blood Levels of Dye in Percentages of Initial Concentration

Patient Group	*Hours–*	*2*	*4*	*6*	*12*	*24*
No Hepatic Disease n = 18	Range	34–80	34–78	27–60	13–45	9–37
	$\bar{\times}$*	62.1	51.8	42.9	33.7	24.2
	SD**	11.7	11.7	10.6	10.7	9.9
Hepatocellular Disease n = 18	Range	58–77	47–64	37–62	24–58	17–50
	$\bar{\times}$	64.8	55.6	48.0	39.6	30.4
	SD	6.3	5.4	7.4	9.9	9.8
Hepatic Obstructive Disease n = 6	Range	45–75	40–68	33–57	26–49	23–40
	$\bar{\times}$	64.8	55.3	45.5	37.3	30.7
	SD	10.7	9.9	8.7	7.8	3.1

* $\bar{\times}$ = Arithmetic Mean
**SD = Standard Deviation

A statistical analysis of the blood level data (Table 2) indicates that there is no significant difference between the blood levels or the 50-per cent clearance times of patients without hepatobiliary disease, those with hepato-cellular disease and those with obstructive biliary disease.

The urine levels of radioactive Cholografin® in percentages of initial concentration were likewise analyzed (Table 3) and no significant differences were found.

TABLE 2. ANALYSIS OF BLOOD LEVEL DATA

	Best-fitting Exponential Equation by Method of Least Squares*	*Relative percentage concentration at hourly interval*	*Approximate time for 50% level*
No hepatic disease	$y = 59.8\ e^{-0.040\times}$	0.96	4.8 Hrs.
Hepatocellular Disease	$y = 63.0\ e^{-0.033\times}$	0.97	6.8 Hrs.
Hepatic obstructive Disease	$y = 60.8\ e^{-0.031\times}$	0.97	6.0 Hrs.

* × = Hours after administration
y = Percentage of original

The above results would seem on superficial consideration to be disturbingly at variance with the general knowledge that iodipamide is removed more slowly from the blood stream in people with liver disease than normal people and also excreted more completely in the urine by people with liver disease than by normal people. In fact, in the routine use of iodipamide for cholangiography, 4 to 8 grams of the chemical are used. In the use of radioactive iodipamide usually less than 0.25 mg of iodipamide is used. This tremendous disparity between the challenge that the liver must face in the routine intravenous cholangiography and the minimal challenge the liver faces in the use of the radioiodinated iodipamide sodium as a test may account for the lack of definitive results in the use of this minimal amount of material. The liver even in disease still has such a large amount of ability to function in various directions that this minimal challenge may not bring to light any defect in liver function that is existent.

TABLE 3. URINE LEVELS OF DYE IN PERCENTAGES OF INITIAL CONCENTRATION

	n	range	$\bar{x}$	SD
Patients with No Hepatic Disease	15	2.0–23.5	10.4	5.2
Patients with Hepatocellular Disease	7	2.4–21.9	9.4	6.0
Patients with Hepatic Obstructive Disease	2	5.8–10.5	8.2	2.4

SUMMARY

1) The clearance and excretion of radioiodinated (I^{131}) iodipamide was studied in normal patients and patients with hepatobiliary disease.

2) We found that radioactive (I^{131}) iodipamide in test dosages of 0.25 mg of iodipamide cannot be used to separate patients with normal hepatobiliary function from those that have defects in hepatic or biliary function.

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JOURNAL OF NUCLEAR MEDICINE 3:67, 1962

The Radioisotope Renogram: Advances in Test Substance and Procedure

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The radioisotope renogram is designed to provide rapid, simple comparison of kidney function. This is accomplished by obtaining a radioactivity curve externally over each kidney area after the intravenous injection of certain radioactive substances. Although the principle is simple, there have been major obstacles to the comparison of kidney function by such curves. The obstacles have fallen into two categories: radioactive materials, and the collimation systems employed for their detection.

Radioiodinated substances in general use for the renogram have certain undesirable characteristics. I^{131}-labeled Diodrast is in part removed from the blood by the liver, thus requiring complicated collimation to detect kidney activity while shielding from liver activity.[1-5] Further, a preliminary kidney x-ray is necessary to precisely locate each kidney before the test.[1,3] Diodrast has therefore largely been supplanted by such I^{131}-labeled materials as Miokon, Hypaque and Renografin, which are not taken up by the liver,[6] thus allowing wider-angle collimation perpendicular to the back.

However, these substances are removed from the blood slowly, providing less sensitive evidence of differences in kidney function*.[5] A recently developed substance – I^{131}-labeled sodium o-iodohippurate (Hippuran†)[5,7,8] – eliminates these objections. Hippuran is removed from the blood only by the kidneys and is almost completely cleared from the blood with each pass through the kidney.[9] These qualities allow simplified collimation, sensitive comparison of kidney function and reduced testing time. The blood clearance rate approximates renal plasma flow.

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*The term "function" is used to indicate the rate of uptake of radioactive Hippuran by the kidney. The limitation of this uptake in most instances is probably renal blood flow rather than tubular or glomerular function.

†This material was first made by M. Tubis in the Radioisotope Service, Veterans' Administration Center, Los Angeles. Subsequent material has been kindly supplied through the courtesy of E. R. Squibb and Sons (Dr. Paul Numerof).

With this improved material, curves obtained externally over the kidneys should be identical when kidney functions are identical, provided geometric conditions are equivalent on each side. In practice geometric conditions (kidney position, fat, muscle mass, etc.) are seldom symmetrical; therefore, the curves are often dissimilar. Reproducibility in the same individual is only fair, and it is occasionally difficult to distinguish between differences caused by renal pathology and differences caused by dissimilar geometry. It would therefore be desirable to use a collimation system which reduces geometric differences to a minimum.

At the present time the most widely used collimation is the type which was developed when it was necessary to exclude the liver radioactivity of Diodrast. A small probe with a 1½ inch aperture and with the crystal 1½ inches from the skin is placed directly over each kidney, positioned by x-ray. The claimed advantages of this method are that the "kidney-background ratio" is increased allowing a truer comparison of kidney function, and the radioactivity is decreased.

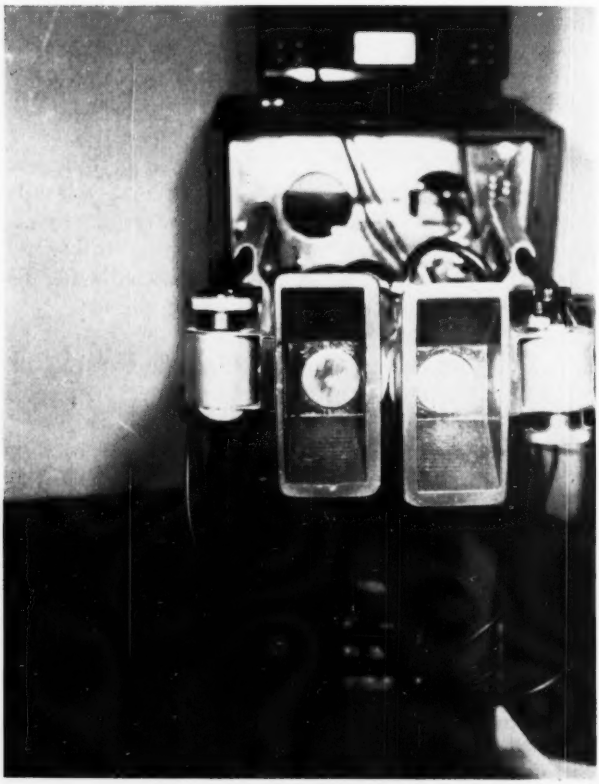

Fig. 1. New wide-angle collimator. For dimensions, see text.

There has been growing dissatisfaction with this collimation system. In most clinical situations it is difficult, time consuming and costly to obtain a preliminary x-ray. Further, the radiation of the x-ray itself is several times the radiation of the renogram. In addition, the reproducibility of results in serial studies has not been satisfactory. For these reasons a "blind" technique was developed by us[5] and by others[2,10] using a wider diameter probe aperture (about 2½ inches), placing its center opposite the average kidney positions. This has considerably simplified the renogram procedure, and the curves have been comparable to those obtained with a small aperture, thus eliminating the necessity for a routine preliminary x-ray.

Despite the enlarged aperture, however, it has remained difficult to obtain consistently equal curves in the presence of equally functioning kidneys. In order to circumvent these geometric artefacts, two collimation changes seemed theoretically advisable. The first was to increase the skin-to-crystal distance, taking advantage of the fact that at a greater distance from the radioactivity

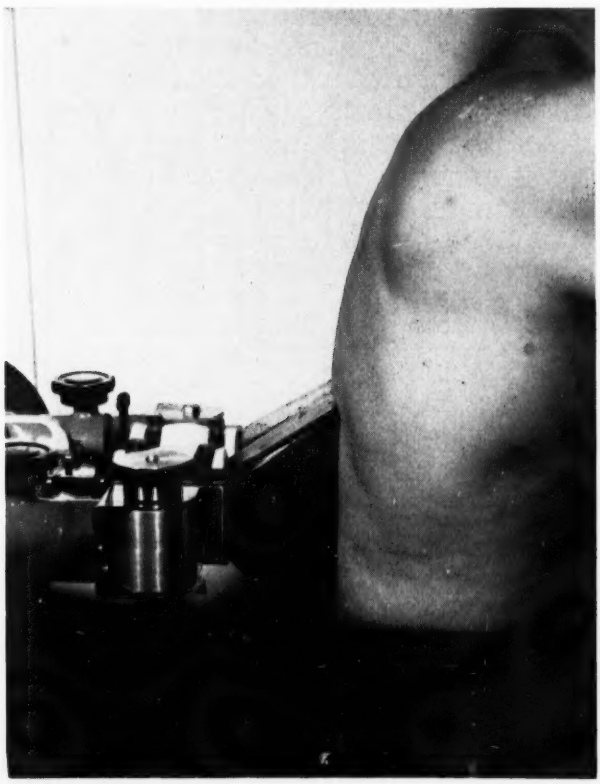

Fig. 2. Position of collimator. Inferior edge is placed at the iliac crest with medial edges approximated.

source, geometric variations make less difference in the count rate. The second was to use collimation so wide that any possible kidney position (except intrapelvic) would be included in the sensitive area of the crystal, while still providing good shielding between the two kidneys.

METHOD

New collimators were devised incorporating the preceding principles (Fig. 1). These were rectangular at the skin surface (2½ x 6 inches) sloping back to a 1-inch crystal recessed 3 inches within the lead shield. The medial wall was ½ inch thick while the lateral wall was ¼ inch thick.

The inferior collimator borders were placed at the iliac crest, bringing the crystals opposite the normal kidney position (Fig. 2).

After the intravenous administration of 30-60μc I^{131}-labeled Hippuran (depending on the instrument scale used as well as body size and contour) a curve

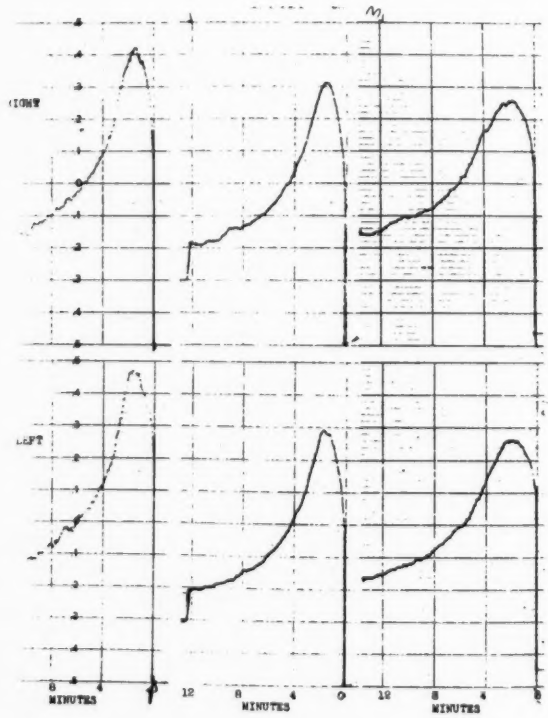

Fig. 3. Normal renograms obtained with new collimator.

Left **60μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 30 sec. (R.W.)**

Middle **50μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 30 sec. (R.W.)**

Right 60μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 10 sec. (J.F.)

was obtained from each kidney area through a rate meter and linear recorder. Fifty μc I^{131}-Hippuran has been calculated to give 0.02 rad to the bladder wall.[11]

RESULTS

Examples of patterns obtained from normal individuals with the new collimator are shown in figure 3. Renogram patterns obtained with this collimator could not be distinguished from those obtained with a collimator having a 1½ inch aperture, 1½ inch recession of the crystal, and x-ray localization (Fig. 4). With no collimation at all except for a midline lead plate, the curves were also comparable, except that there was a slower reduction in radioactivity levels after the peak had passed (Fig. 4). This probably represents accumulating bladder

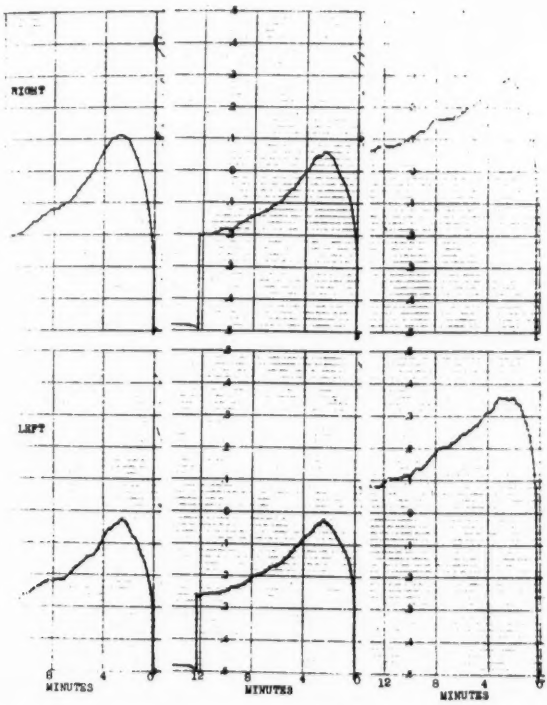

Fig. 4. Comparison of renograms in the same individual with different techniques. Kidneys were in normal position by x-ray.

Left **Aperture 1½″. Crystal withdrawn 1½″. 40μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 30 sec.**

Middle **New wide-angle collimator (see text for dimensions. Crystal withdrawn 3″ from skin). 40μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 30 sec.**

Right **No collimation except for midline lead plate. Crystal 3″ from skin.**

radioactivity, which is excluded by the other techniques. No evidence could be found that kidney-to-background ratio differences were of any practical importance.

Exclusion of radioactivity from the opposite kidney was excellent with this collimator, as it has been with previous systems (Fig. 5).

The shape of curves on a linear plot varied not only with differences in kidney function but also with the amount of radioactivity given, the amount of body fat and muscle, the total blood volume, the state of hydration and other factors. It was evident throughout these studies that the contour of the curves could not be used to estimate total combined renal function except in the presence of gross abnormalities.

The most striking findings in a large number of renograms using the new

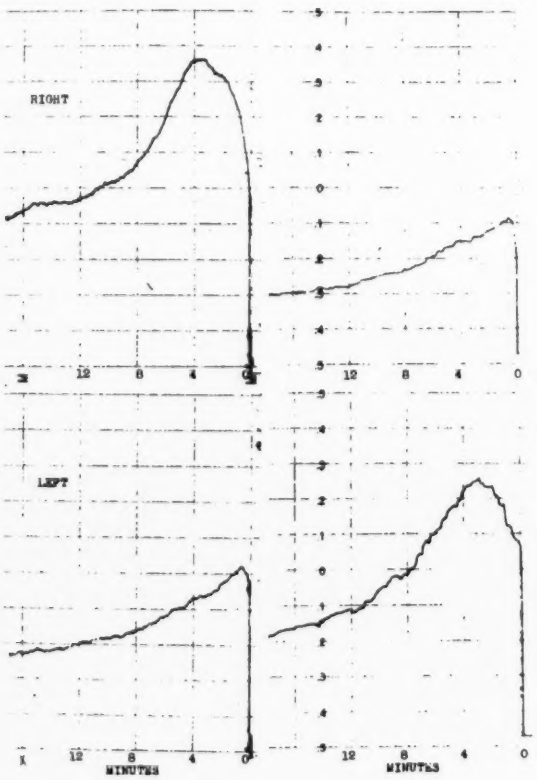

Fig. 5. Renograms obtained with one kidney absent.

Left **New collimator (see Figs. 1, 2). Left kidney absent. 50μc I^{131}-Hippuran. Scale, 30K c/m. Time constant, 30 sec.**

Right **Collimator aperture 2½″. Crystal withdrawn 2″. Right kidney absent. 20μc I^{131}-Hippuran. Scale, 72K c/m. Time constant, 40 sec.**

collimator were improved reproducibility and comparability of the curves in the presence of equally functioning kidneys. Minor discrepancies were present, however, and a further collimator modification was subsequently made which has the same dimensions at the skin but has the crystal recessed 6 inches instead of 3 inches (Fig. 6). Preliminary results with this modification indicate even further improvement in reproducibility and comparability.

DISCUSSION

Since the development of the radioisotope renogram five years ago,[12,1] there has been progressive improvement in both radioactive materials used and in equipment for radioactivity detection.

Efforts to improve material have been aimed towards obtaining a gamma-emitting substance which is rapidly removed from the blood by the kidneys only. Such a substance is now available in I^{131}-labeled Hippuran. The fact that Hippuran is extracted from the blood almost completely on each pass through the kidney makes its blood clearance a measure of effective renal plasma flow. This may be of special significance in the correlation of unilateral kidney ischemia with hypertension. Hippuran increases the sensitivity of the renogram by its rapid kidney uptake and excretion;[5] and since there is no radioactivity in the liver, the detecting probes may be placed perpendicular to the back, using wider collimation.

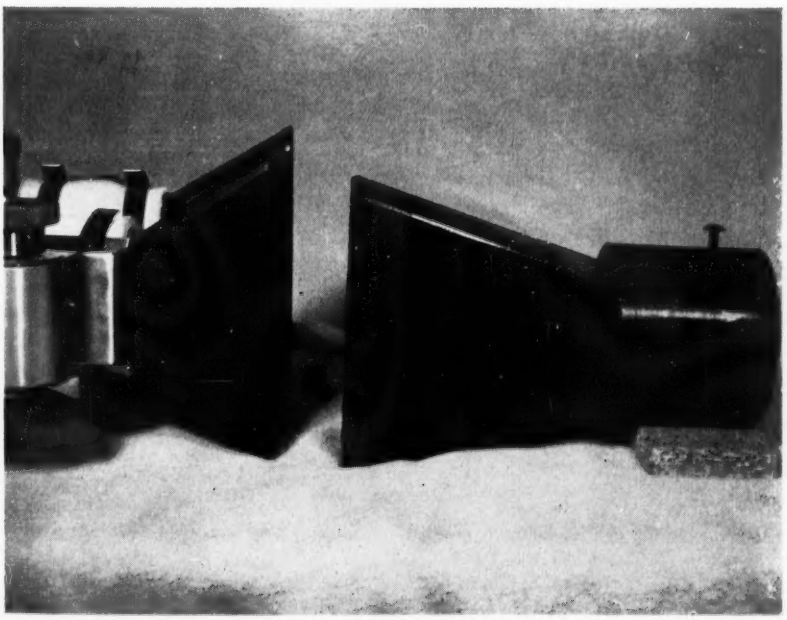

Fig. 6. ***Left*** **New collimator with crystal recessed 3″ within the lead shield.**
Right **Further modification with crystal recessed 6″.**

Efforts to improve equipment have been aimed towards providing a system which will faithfully and simply compare the function of the separate kidneys. The collimation design described here, with a much enlarged field of "vision" and a greater skin-to-crystal distance, simplifies probe placement and increases accuracy of kidney function comparison. There appears to be no advantage to precise placement of small probes directly over the kidneys to reduce the kidney-to-background ratio. Since probes with small apertures provide no more useful information than probes with wide-angle collimation and are more difficult to position, it is suggested that they be abandoned.

Attempts to estimate combined kidney function by comparing obtained curves with "normal" standards have been disappointing. Since so many variables go into producing the height and shape of the curves, it remains hazardous to estimate total renal function by the renogram except where gross abnormality is present.

Improved material and instrumentation have brought the radioisotope renogram to a state of high sensitivity and reliability when used to compare one kidney with the other. Long-term studies are now being undertaken to determine its proper position among other methods of studying individual kidney function.

SUMMARY

As a minimum ideal the radioisotope renogram should provide a rapid, simple method for determining comparative kidney function by external body counting. Since the advent of I^{131}-labeled iodohippurate (Hippuran), which is removed rapidly from the blood by the kidneys only, testing time has been shortened and comparison of kidney function has been made more sensitive. Since there is no uptake of Hippuran by the liver, wide-angle blind collimation is feasible.

Present collimation systems have not provided routinely reproducible and valid comparison of kidney function, chiefly because of emphasis on placing small probes precisely over the kidneys to increase the "kidney-background ratio", and keeping the crystal close to the skin to reduce administered radioactivity. Both of these factors greatly magnify geometric differences of kidney position and individual body contour. In order to minimize these factors, a new collimator was designed. It was rectangular at the skin, 2½ x 6 inches, sloping back 3 inches (later 6 inches) to the crystal. This collimation has greatly enhanced simplicity of probe placement, reproducibility and valid comparison of kidney function.

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JOURNAL OF NUCLEAR MEDICINE 3:76, 1962

Myocardial Scanning With Rubidium-86[1,2]

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PRELIMINARY NOTE[3]

INTRODUCTION

Radioactive iodine labelled human serum albumin has been used successfully in combination with the photoscanner to delineate the human cardiac cavities in health and disease (1). Burch and associates (2,3), investigating the use of Rubidium-86 as a tracer for potassium in dogs and men, found that Rb^{86} is rapidly cleared from the blood and concentrates in the myocardium. We wish to report an investigation of the possible use of Rb^{86} for photoscanning the myocardium in vivo.

METHODS

The general plan of the experiments included injection of Rb^{86} into dogs, sacrifice and counting of radioactivity in tissue samples, with scintiscanning performed before and/or after sacrifice.

Tissue Counting

Four normal mongrel dogs weighing 7.8 kilograms to 9.9 kilograms were injected intravenously with 100 to 500 μc of $Rb^{86}Cl$[4] (as shown in Table 1), and sacrificed 1½ to 4¾ hours later with a lethal intravenous dose of pentobarbital. The anterior descending branch of the left coronary artery was ligated in three other dogs just below the bifurcation of the left coronary artery 1 to 2 days before the administration of Rb^{86}. Two hundred mg to 2 gm of various tissues (as in

1. From the Departments of Internal Medicine (Clinical Radioisotope Unit), Pharmacology and Radiology, The University of Michigan, Ann Arbor, Michigan.
2. This project was supported in part by the Isotope Unit Research Fund.
3. Preliminary note: See page 25.
4. Abbott Laboratories, Oak Ridge, Tennessee. Specific activity 8.2 to 13.8 mc/mg of RbCl.

Table 1) were removed, dissected free of adjacent tissues, blotted and counted in a scintillation well-type counter. In dogs with myocardial infarcts, appropriate sections of normal and abnormal myocardium were excised, counted, fixed in formalin, and subjected to histologic examination by a pathologist with no knowledge of the relative radioactivity concentrations of the specimens. Multiple samples of left ventricle were studied in three of the normal dogs to allow an estimate of normal variation in myocardial Rb^{86} uptake.

Photoscanning

All of the hearts were scintiscanned with a photoscanner.[1] A total of 7 scans of living hearts in situ in intact dogs, 2 scans of dead hearts in situ and 4 scans of excised hearts were performed. Scans of the living heart were performed under pentobarbital anesthesia, 20 minutes to 3½ hours after injection of Rb^{86}, before sacrifice for the tissue studies described above. Scanning was performed with the dog in the supine position and the collimator placed as close to the anterior chest wall as possible. The procedure finally adopted was to scan from the xiphoid to the sternal notch for a period of 40 minutes, beginning 20 minutes after injection of Rb^{86}.

In three of the normal dogs, the general experimental protocol was modified by additional studies. In one dog, the sternal notch and xiphoid were marked with tacks before scanning. After scanning the dog was sacrificed and the scan repeated. With the tacks in positions, the anterior chest wall was removed and the pericardium opened. With the aid of perpendiculars from a thread stretched between the two tacks, the exact projections of the base, apex and lateral margins of the heart were fixed on the scintigram. The heart was then excised and its entire content of blood emptied into a beaker. The emptied heart and heart's blood were scanned separately using identical settings on the photoscanner.

In another dog an anteroposterior chest roentgenogram was taken after scanning and before sacrifice. In a third dog the chest was scanned before and after removal of the heart.

RESULTS

Tissue Concentrations

The normal left ventricular myocardial Rb^{86} concentration averaged 57 times greater (range = 34 to 88) than the concentration of Rb^{86} in the blood at the time of sacrifice, as shown in Table 1. The differential concentration in different areas in the normal left ventricular myocardium varied in the same heart by only 12 per cent (range = 7 to 15%). The differential concentration in left ventricular myocardial infarcts, however, was 46 to 68 per cent that of normal left myocar-

1. Picker Magnascanner, Picker X-Ray Corporation, White Plains, New York.

TABLE 1. DISTRIBUTION OF Rb^{86} IN DOG TISSUES

Dog #	*Status*	*Dose of Rb^{86} (μc)*	*Time between Rb^{86} injection and sacrifice*	*Conc of Rb^{86} (cpm/gm wet weight)*											
				Heart					*Blood*	*Liver*	*Lung*	*Aorta*	*Rib*	*Skel. Muscle*	*Dia-phragm Muscle*
				Left Ventricle			*Rt. Ventr.*	*Auricle*							
				Normal	*Ischemic (non-infarcted)*	*Infarct*									
1	Cor. art. ligation 1 day previously	200	30 min.	28300	26900	19200	23100	22900	325	10400	10100	5200	2900	4200	—
2	Cor. art. ligation 2 days previously	100	30 min.	16200[a] 17200	6300	10500 4600	12100	16200	276	7700	7800	881	2400	3800	....

3	Normal	500	1 hr. 10 min.	34800 37600 42400	. . .	. . .	36700	31500 (left) 30000 (rt.)	626	22600	30400	5400	3800	12000	18900
4	Normal	500	1 hr. 10 min.	35200 37500	. . .	. . .	38900	32900	557	30400	9700	. . .	. . .	5000	14000
5	Cor. art. ligation 2 days previously	500	2 hrs. 45 min.	26000	27200 25300	25500	28200	. .	753	26300	16100	. . .	4800	14500	. . .
6	Normal	500	4 hrs. 45 min.	17900	. . .	. . .	. . .	. . .	279	22000	12000	. .	8300	14300	. . .
7	Normal	500	4 hrs. 45 min.	22000 24500 26200	. . .	. . .	27300	23400 (left) 21300 (right)	652	21800	14000	12500	5800	23500	19700

•Where several counts are listed for one dog's tissue, each refers to a separate sample.

dium except in dog #5, in whom only minimal necrosis was found on histologic examination of the myocardial sections. In the two specimens within one infarct in dog #6, the differential concentration of Rb^{86} varied from 28 to 63 per cent of the concentration in normal left ventricular myocardium. Although the differential concentration of Rb^{86} in right ventricular and auricular myocardium tended to be slightly lower than in left ventricular myocardium, especially at the shorter intervals between tracer dose and sacrifice, this difference was not significant. The liver concentration of Rb^{86} was lower than heart in 5 of 7 dogs. The lung concentration of Rb^{86} averaged 54 per cent of heart concentration (range = 27 to 80%). The concentration of Rb^{86} in thoracic aorta, ribs, skeletal muscle and diaphragm was also less than in the heart. Skin, fat, trachea, esophagus, pericardium, and pleura contributed little radioactivity. No definite relationship was observed regarding time from administration of dose to time of sacrifice and absolute or relative tissue concentrations of Rb^{86}.

Photoscanning

Figure 1a is an in vivo photoscintigram of the beating heart in intact dog #3. Figure 1b is the same photoscintigram with the exact outline of the determined projection (see "Methods") of the heart circled. The principal adjacent concentration of radioactivity was found to be in the liver. All six additional photoscintigrams in three other living dogs were similar. When the heart was removed from one dog (#4) immediately after in vivo scanning, the repeat scintigram of the chest showed absence of the radioactivity attributed to the heart in the first scan. A photoscintigram of the removed heart's blood and also of the emptied heart demonstrated that all detectable density in the scintigram of the intact heart was from the myocardium and not the heart's blood. The heart shadow on the chest roentgenogram of the living dog also coincided with the outline of the heart shown in the photoscintigram.

DISCUSSION

These data show that the radioactivity concentration in the dog thoracic area after a tracer dose of Rb^{86} is primarily in the myocardium and the liver. The heart's blood contributes negligibly to the cardiac photoscintigram. The projection of the heart area has been sharply localized under the conditions used here.

Since concentrations of radioactivity within the myocardium of one left ventricle varied normally only 7 to 15 per cent and the differential concentration in infarcted left ventricular myocardium was usually 46 to 68 per cent of the concentration in normal left ventricular myocardium, infarcted muscle will usually show a concentration of radioactivity that is more than 15 per cent below the concentration in adjacent normal heart muscle. Since our photoscanner can detect differences in tissue concentrations of as little as 15 per cent and picture these differences as contrasted densities, it is theoretically possible to demonstrate a myocardial infarction by photoscintiscanning. From other studies with this photo-

scanner (4), it is unlikely that infarcts smaller in diameter than 1 × 1 cm will be capable of detection. We are at present determining the size of the infarct that can be detected in dogs before proceeding to man. We have already demonstrated an infarct measuring 1¾ × 2 cm in a scintigram of an excised heart. Further trials might also profit by the use of other gamma-emitting isotopes having a tissue distribution similar to potassium, such as Caesium-134.

Addendum: Since submission of this manuscript we have also injected Hg^{203}-labeled chlormerodrin (Neohydrin) into dogs after coronary artery ligation. With this compound, we have been able to demonstrate myocardial infarcts as *positive* areas of increased radioisotope concentration in scans of the beating hearts of the living, intact dogs. This work is the subject of a separate report (5).

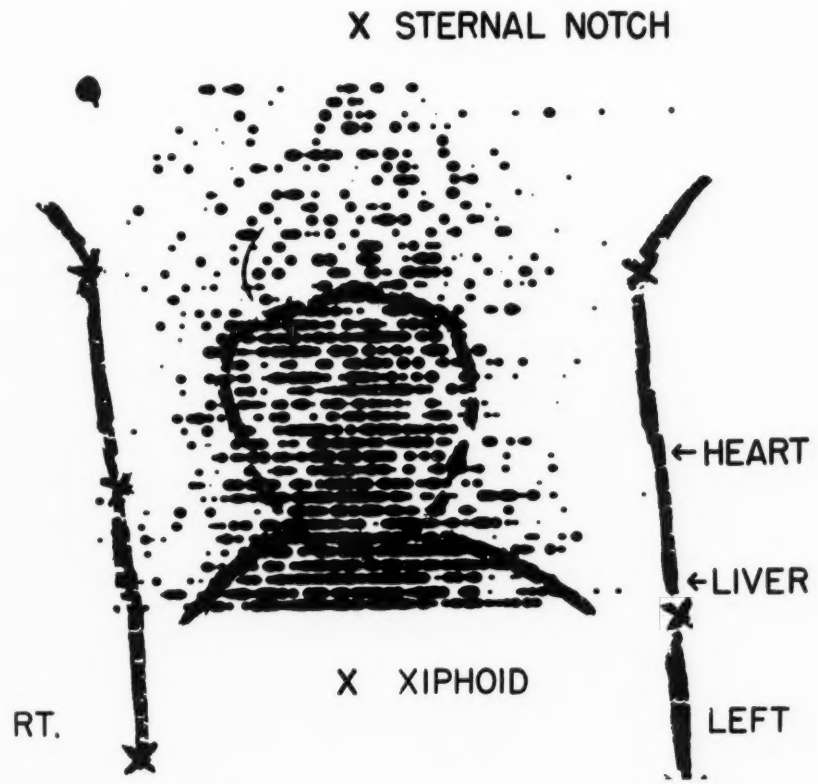

Fig. 1a. Myocardial scan of normal, anesthetized dog. The scanning began 20 minutes after intravenous injection of $Rb^{86}Cl$ (see text). The lateral contour lines outline the body wall.

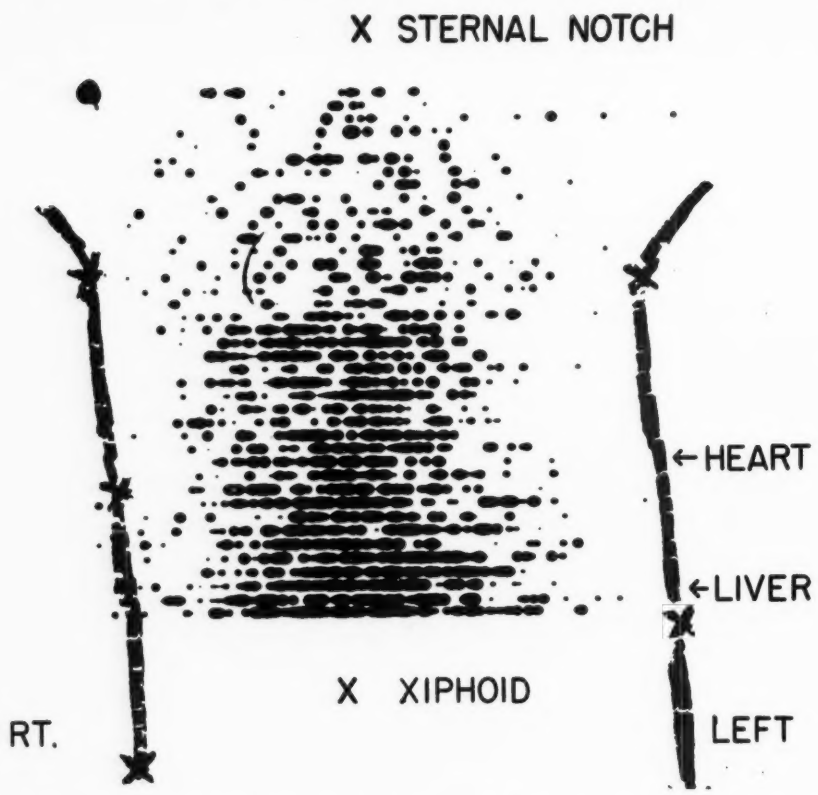

Fig. 1b. Same scan as in Fig. 1a, with the outline of the heart and diaphragm drawn in. The outline was determined by measurements made as described in the text.

ACKNOWLEDGEMENT

The technical assistance of Barbara J. Walker, B.S., is acknowledged.

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JOURNAL OF NUCLEAR MEDICINE 3:83, 1962

Radiomercury (Hg^{203}) Labeled Neohydrin:[1,2] A New Agent for Brain Tumor Localization

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INTRODUCTION

In spite of the many recent advances in scanning instrumentation, the preoperative detection and localization of brain tumors with radioisotopes is still relatively difficult. Basically the problems stem from the nonspecificity of the tracer agents used; only a very minute fraction of the isotope injected is fixed in the tumor area. Such localization as does occur is not based on tumor metabolism, but rather on a local breakdown of the "blood-brain barrier" which permits pooling of materials ordinarily excluded (1,2).

Ideally the search for new agents should be aimed at the discovery of materials which are actively concentrated by tumor metabolic processes. Unfortunately, in spite of widespread effort in this field, no such compounds have been found. The work reported in this paper is confined to improvements in brain tumor localizing materials utilizing the non-specific "blood-brain barrier" breakdown phenomenon.

DISADVANTAGES OF I^{131} ALBUMIN

The agent most commonly employed for brain tumor localization with gamma emitting isotopes is I^{131} labeled albumin. The physical properties of I^{131} and the biological properties of albumin are not optimal for tumor detection.

In any scanning procedure it is essential to maximize the detection of counts from the target area and to minimize counts originating from outside the target area. This is achieved by heavy shielding of the detector, focusing collimators, and rejection of scattered and degraded radiation by pulse height analysis. The major gamma ray of I^{131} is at .36 Mev (87%) but there are two gamma rays with higher energies, .64 Mev (9%) and .72 Mev (3%). The energy

1) From the Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo.

2) Presented in part at the 6th Annual Meeting, June, 1959, and the 7th Annual Meeting, June, 1960, of the Society of Nuclear Medicine.

of the principal gamma ray is somewhat high for effective collimation and shielding with lead (3), but the most important physical disadvantages of I^{131} stem from the appreciable fraction of gamma rays at the higher energies. These high energy gamma rays can originate outside of the target area but reach the detector by penetrating shielding, crossing collimator septa and by scattering into the collimator field. In a fraction of the scattering processes the incident gamma ray loses just enough energy to be counted in the .36 Mev photopeak. While this is an inefficient process, the bulk of the radioisotope is not in the volume seen by the collimator and even improbable events give significant count rates. In actual practice, approximately one-half of the total count rate is from this source when the 61-hole ORNL lead focusing collimator (4) is used.

The biological properties of albumin are also disadvantageous for tumor localization. At the time of scanning (24 - 48 hours after injection) 80-90 per cent of the administered I^{131} albumin is still in the body and 40-50 per cent remains in the blood (5,6). This high "body background" of radioactivity reduces the target : non-target ratio between tumor and normal brain. Tumor localization in the region of large blood vessels (superior sagittal sinus, transverse sinus, etc.) is particularly difficult. In addition to the problems associated with the higher radioactivity of normal brain structures, the failure of I^{131} albumin to be excreted accentuates the problems arising from scattered radiation and shielding penetration.

PHYSICAL ADVANTAGES OF Hg^{203}

A search of the catalogs of available radioactive isotopes for a nucleide with suitable gamma ray emission, half-life, specific activity, etc. yields one outstanding candidate, Hg^{203}. Table 1 compares the physical properties of I^{131} and Hg^{203}. The single line emission of Hg^{203} at .28 Mev minimizes the problems of scattering and penetration associated with the spectrum of I^{131}. The lower energy of the β particles from Hg^{203} reduces the radiation dose to the patient. This is partially offset by the longer physical half-life of the Hg^{203}, but this disadvantage can be overcome by incorporation of the Hg^{203} into a compound with a short biological half-life.

TABLE 1.

PHYSICAL PROPERTIES OF Hg^{203} AND I^{131}

	Beta	*Gamma*
I^{131}	.61(87%)	.36(87%)
(8.0 Days)	.34(9%)	.64(9%)
	.25(3%)	.72(3%)
	.82(1%)	.16(1%)
Hg^{203}	*Beta*	*Gamma*
(45.8 Days)	.21(100%)	.28(100%)

The improvement in target : non-target ratios resulting from the physical advantages of Hg^{203} are difficult to estimate and will vary depending on the collimator and shielding employed. Table 2 contains the data from a simple experiment to estimate the improvement attributable to decreased crossing of collimator septa and scattering into the collimator field. A 6″ cubic plastic phantom is filled with a solution containing .01 uc/cc representing normal brain background activity. The count rate is measured using a 61-hole, 3″ focusing lead collimator with a 3″ × 2″ NaI (T1) crystal. Pulse height analysis is used to minimize the contribution of scattered radiation. Then a 1″ diameter spherical "tumor" containing .02 uc/cc is placed at the center of the cube and the count rate redetermined. This is done with I^{131} and Hg^{203}. In the case of I^{131} the "tumor" causes a 10% increase in count rate. With Hg^{203} the increase is 13%; a 30% improvement in target : non-target ratio. Additional increases in target : non-target ratios would be observed in clinical practice where radioactivity located outside of the head would contribute to the count rate by penetration of shielding and by scatter.

BIOLOGICAL ADVANTAGES OF NEOHYDRIN

Having chosen Hg^{203} for its physical properties, it remained to prepare a mercury compound with suitable biological properties. The most important consideration is the biological half-life of the compound. This must be short enough to permit the clearance of the bulk of the injected material before scanning but not so short that the radioactivity is completely cleared from the body before scanning can be accomplished. The exact optimum is difficult to estimate but it is probably of the order of hours; clearance times of minutes being too short and days being too long. In addition, the compound must be non-toxic, easily synthesized with high specific activity, have a long shelf life, and the mercury must be firmly bound.

After preliminary trials with ionic mercury and various chelated forms, it was concluded that suitable biological properties could be achieved only with some form of covalent organic mercury compound. Their rapid clearance from the body (7) and long record of low toxicity suggested the mercurial diuretics as suitable compounds. Neohydrin (3-chloromercuri-2-methoxypropyl-urea) was

TABLE 2.

TARGET: NON-TARGET RATIOS WITH Hg^{203} AND I^{131} IN A PHANTOM

	No "Tumor"	*With "Tumor"*	*% Increase*
Hg^{203}	190 c/min	215 c/min	13
I^{131}	270	297	10

Phantom: 6″ cube; .01 uc/cc
"Tumor": 1″ sphere; .02 uc/cc
Collimator: 61 hole, 3″ focus, lead.

chosen because it is easy to synthesize. The compound was prepared by the addition of radioactive mercuric acetate to allylurea (Fig. 1) and treatment of the subsequent product with sodium chloride. A micro-adaptation of a procedure suggested by Lakeside Laboratories was used (8).

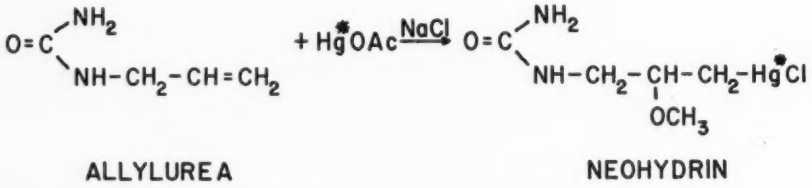


Fig. 1. Synthesis of Hg-203 Neohydrin

The clearance of Hg^{203} Neohydrin was measured in a series of patients. Figure 2 shows the rapid disappearance from the blood. Less than 10% remains after 5 hours. With iodinated human serum albumin up to 90% of the

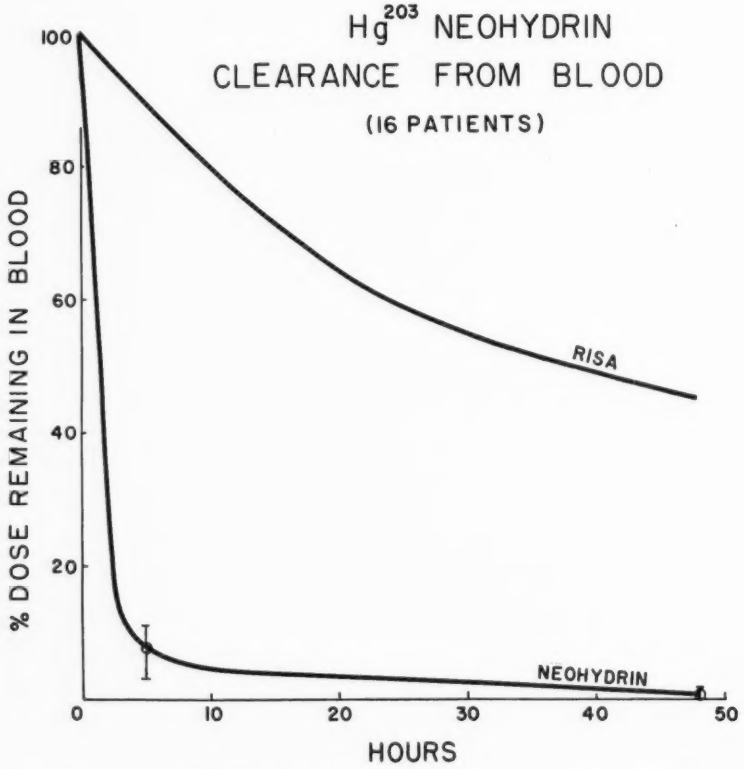


Fig. 2. Blood clearance of Hg-203 Neohydrin and I-131 human serum albumin (Risa)

injected dose is present at this time (5,6). Figure 3 compares the cumulative urinary excretion of Neohydrin with that of iodinated human serum albumin. Almost half of the Neohydrin is excreted during the first eight hours; the retention of albumin is almost complete at this time.

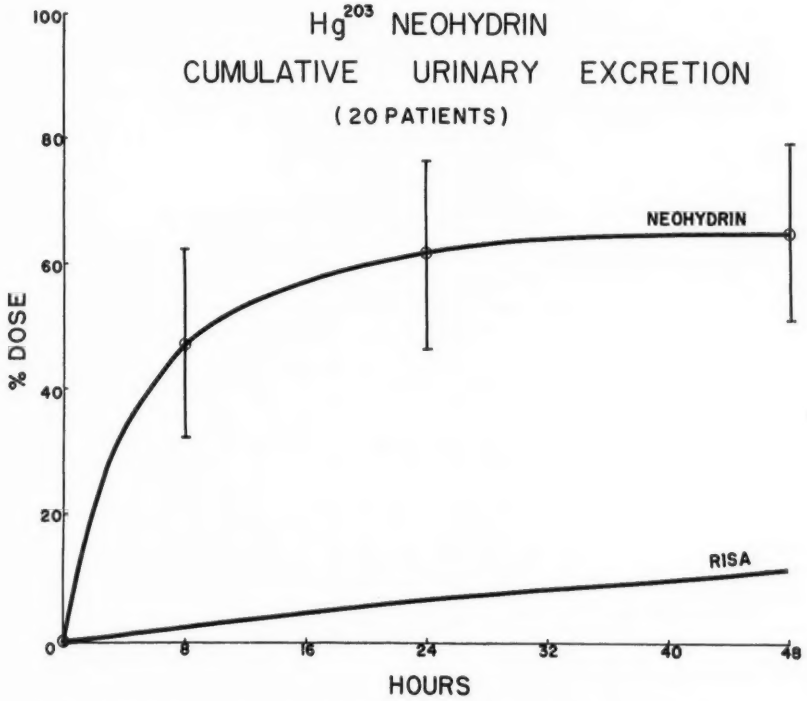


Fig. 3. Cumulative urinary excretion of Hg-203 Neohydrin and I-131 human serum albumin (RISA)

WHOLE BODY RADIATION DOSE FROM Hg^{203} NEOHYDRIN

Without whole body counts on the long term retention of the Hg^{203} not excreted during the first day or two following administration, it is difficult to calculate the radiation delivered by a diagnostic dose of Neohydrin. By combining the data from this laboratory on the excretion during the first 48 hours after administration with reports from other laboratories (7,13) on the long term excretion of closely related mercurial diuretics (Thiomerin and Mercurhydrin) a rough estimate can be made. The excretion of the Hg^{203} can be approximated by a two segment curve, with about 50 per cent of the dose excreted during the first 8 hours and the remainder with a half-time of 3 days. The half-life of 3 days is derived from data on mercurials other than Neohydrin, but since Neohydrin behaves like these compounds for the first 2 days and no

differences were observed between the two, extrapolation of these data to predict Neohydrin excretion is probably reasonable. The calculation is based on uniform distribution in a 70 kilo cylinder with a height 3 times the radius. This distribution is not strictly true for Neohydrin but the only known deviation is the long term kidney retention discussed below.

$D_{\beta+\gamma} = 0.5$ mrad/hr. or 12 mrad/day

Dose = 10 uc/kg

1st 8 hours:

$$.5 \frac{\text{mr kg}}{\text{hr.uc}} \times \frac{10 \text{ uc}}{\text{kg}} \times 8 \text{ hours} \times 1.44 \times \tfrac{1}{2} = 29 \text{ mrad}$$

8 hours to Total Decay:

$$\frac{12 \text{ mr kg}}{\text{day uc}} \times \frac{5 \text{ uc}}{\text{kg}} \times 3 \text{ days} \times 1.44 = 260 \text{ mrad}$$

Total Dose = 290 mrad/patient.

This is substantially less than the 700 mrad delivered by a brain tumor localization dose of 5 uc/kilogram of I^{131} human serum albumin.

KIDNEY RETENTION OF Hg^{203} NEOHYDRIN

While the excretion of most of the administered Hg^{203} Neohydrin is relatively prompt, a fraction of the dose is firmly bound in the kidneys. Figure 4 shows the retention by the kidneys as measured by external counting in 10 patients. The quantity remaining was estimated from comparison of patient counts and phantom counts. In one case it was possible to obtain autopsy samples within one day after external counting and the estimation of the residual dose as measured in these samples under known geometry confirmed the *in vivo* counts. About 10 per cent of the dose sticks in the kidneys with a biological half-life of 28 days. The radiation dose delivered to the kidneys is 35 - 40 rad from a brain scanning dose of 10 uc/kilo.

Several procedures for reducing the uptake and retention by the kidneys were tried but only one has had significant effect. Administration of 1 cc of Mercurhydrin (39 mg. Hg) on the day before scanning blocks the sites of uptake in the kidney and causes a 3-fold reduction in the retention of Hg^{203} Neohydrin in most patients (Fig. 4). Mercurhydrin is used as the blocking agent because it is readily available in a form suitable for injection. Presumably any mercurial diuretic would be effective. Blocking with Mercurhydrin reduces the kidney radiation dose 12 - 13 rad.

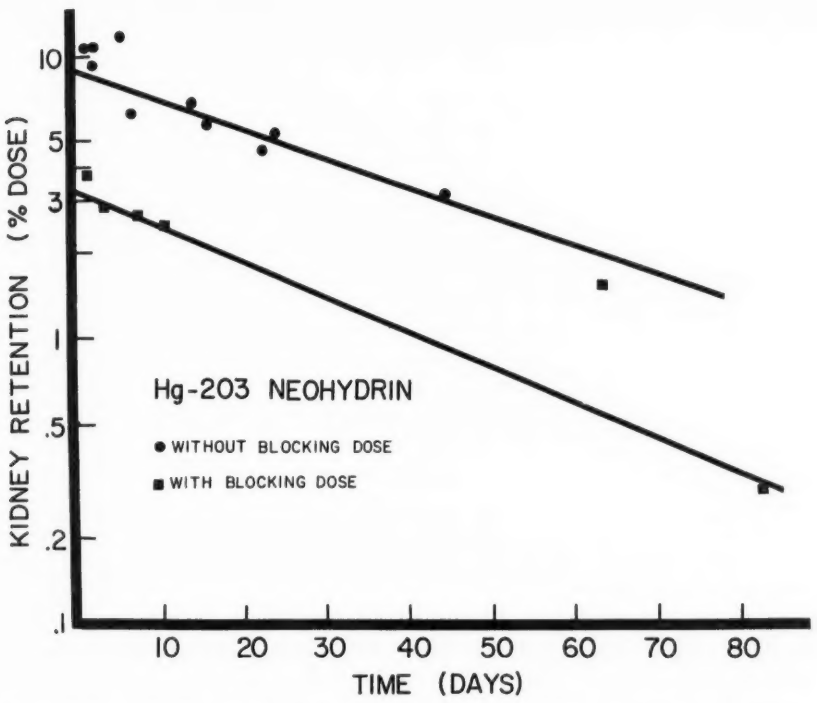


Fig. 4. Kidney retention of Hg-203 Neohydrin. (Blocking dose is 1 cc of non-radioactive Mercurhydrin, I.M., on day before Hg-203 Neohydrin.)

The administration of dimercaprol (BAL), or flushing doses of Neohydrin or Mercurhydrin after scanning had no significant effect on kidney retention. We are currently investigating the use of D-penicillamine, EDTA and DTPA for removing retained mercury.

CLINICAL PROTOCOL

Based on the above excretion data and on preliminary clinical trials (9,10,11) the following scanning protocol was adopted. On the day before scanning 1 ml Mercurhydrin is given intramuscularly to minimize the renal uptake of Hg^{203}. A dose of 10 uc/kilogram of Hg^{203} Neohydrin (specific activity less than .05 mc/mg) is administered intravenously 4 or 5 hours before the start of scanning. The photoscanning system used is essentially that described previously (12). With the Oak Ridge 61-hole, 3-inch lead focusing collimator and a 3″ × 2″ NaI (T1) crystal, count rates over the normal brain are 150 - 200 counts per minute. This is less than half of the count rate observed with an equivalent dose of I^{131} albumin. This reduction in counts can be attributed principally to the reduction of "background" due to the physical and biological advantages of Hg^{203} Neohydrin discussed above.

CLINICAL COMPARISON OF Hg^{203} NEOHYDRIN AND I^{131} ALBUMIN

The physical and biological advantages of Hg^{203} Neohydrin should, of course, be reflected in improved scans. The variability of size, shape, location and concentrating ability between brain tumors makes evaluation of a new agent for brain tumor localization extremely difficult. To minimize this problem Hg^{203} Neohydrin was compared to I^{131} albumin by scanning patients with both agents one or two days part. Neohydrin was administered first and scans obtained after 4 - 8 hours. After scanning, the I^{131} albumin (5 uc per kilogram) was given and scanning repeated after 24 - 48 hours. With pulse height analysis the residual Hg^{203} has no effect on the I^{131} scan.

The scans obtained with I^{131} albumin and Hg^{203} Neohydrin were compared in over 100 patients. In almost every case the Neohydrin scans were as good as the albumin scans. In one-quarter to one-third of the scans the Neohydrin gave more readily interpretable scans. In about 5-10 per cent of the cases a diagnosis could be made from the Neohydrin scans but not from the albumin scans. Improvements in the visualization of both primary and metastatic lesions were noted, but the increased definition was seen more often in primary tumors. The follow-up time has been too short to evalute the overall accuracy of brain tumor localization with Hg^{203} Neohydrin. Using I^{131} albumin in over 300 cases we have been able to give correct localizations about 85 per cent of the time. Neohydrin should raise this figure somewhat but room for improvement is rather limited.

In one case it was possible to obtain tissue samples at surgery performed at what would have been the optimum time of scanning for both agents. I^{131} albumin was given 48 hours before surgery and Hg^{203} Neohydrin 5 hours before surgery. Data from the tissue samples removed are given in Table 3.

TABLE 3.

Hg^{203} NEOHYDRIN AND I^{131} ALBUMIN IN A MENINGIOMA. Hg^{203} NEOHYDRIN GIVEN 5 HOURS BEFORE SURGERY AND I^{131} ALBUMIN GIVEN 48 HOURS BEFORE SURGERY

	% Dose/gram × 10^4		
	Hg^{203}	I^{131}	*RATIO* $\frac{Hg}{I}$
TUMOR	52 ± 4	25 ± 3	2.1
DURA	25	33	.76
BLOOD	18	109	.16

In this 23 gram meningioma, the tumor contained twice as much Hg^{203} as I^{131}. There was remarkable uniformity of distribution in the tumor with both isotopes; the standard deviation of isotope content of the twenty 1 gr. samples measured was about 10 per cent. No sample of normal brain tissue was available but a single sample of dura contained more I^{131} than Hg^{203}. The blood sampled at the time of operation contained 6 times as much I^{131} as Hg^{203}

It appears therefore that Neohydrin remained concentrated in the tumor as well as albumin or better while it was cleared much more rapidly from the blood.

Figures 5, 6 and 7 are selected examples of the improved tumor visualization obtainable with Hg^{203} Neohydrin.

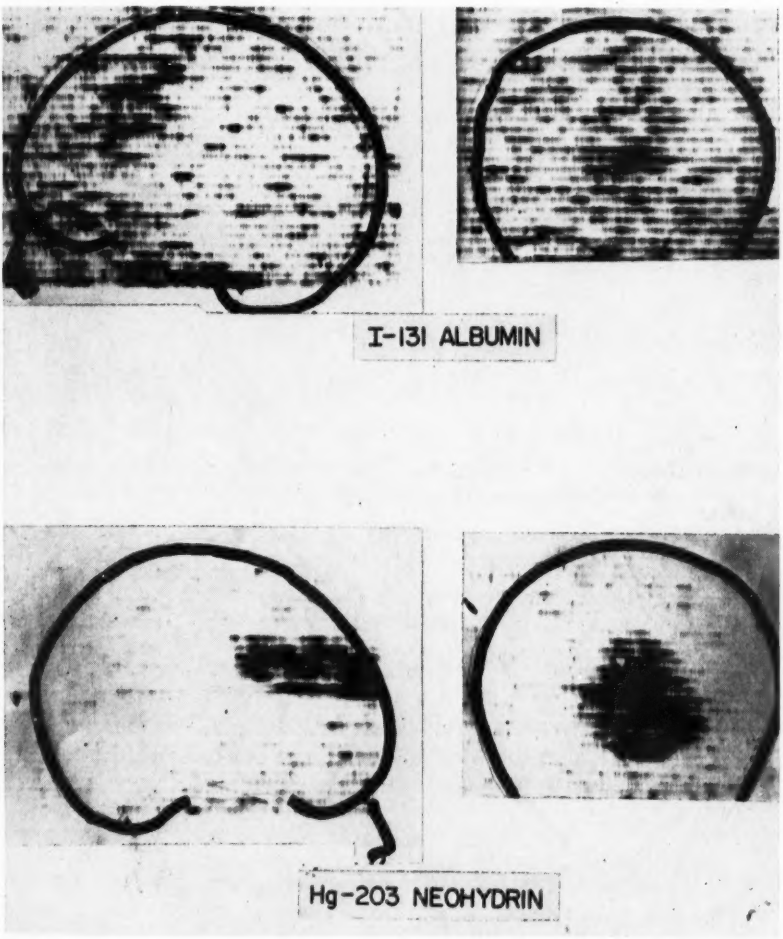


Fig. 5. Lateral and AP photoscans of a patient with a meningioma. Tissue data for this tumor given in Table 3. (See text for scanning protocol.)

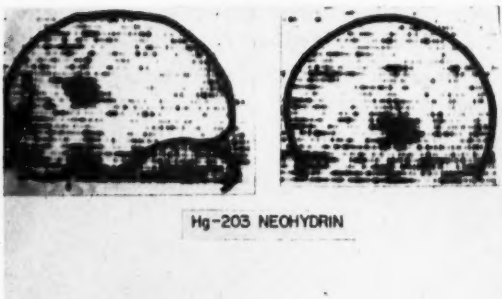
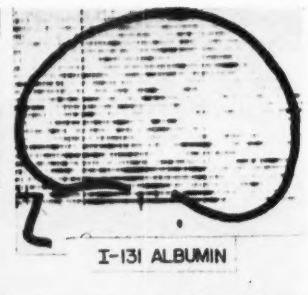


Fig. 6



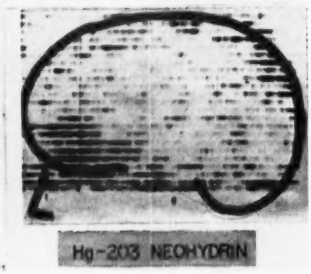


Fig. 7

Fig. 6. Right Lateral and AP photoscans of a patient with metastatic bronchogenic carcinoma. (See text for scanning protocol.)

Fig. 7. Left lateral photoscans of a patient with a metastasis in the frontal lobe from an angiosarcoma. (See text for scanning protocol.)

SUMMARY

Hg^{203} Neohydrin has been developed as a replacement for I^{131} albumin in brain tumor scanning. The rapid clearance of non-localized Neohydrin from the blood and the effectiveness of collimation and shielding on the monoenergetic .28 Mev gamma rays from Hg^{203} result in improved visualization of tumors with this agent. This improvement is significant, but not dramatic.

ACKNOWLEDGEMENT

The physical advantages of Hg^{203} for scanning were first pointed out to us by P. R. Bell, J. E. Francis, Jr. and C. C. Harris of the Oak Ridge National Laboratory Physics Division. This group has often served to catalyze our research and for this we are most grateful.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the May, 1962 issue must be in the hands of the Editor before March 30, 1962.

JOURNAL OF NUCLEAR MEDICINE 3:94, 1962

The Use of the Electronic Digital Computer To Determine Best Fit of Blood Volume Formulas[1]

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New Orleans

Greater utility is achieved for a clinical laboratory measurement such as circulating blood volume if normal limits are known. Circulating blood volume in the normal human adult will vary with physical dimensions, and prediction of normal limits must be related to these physical parameters. A prediction formula from correlation of measured data with physical parameters may be obtained by regression analysis. Since a review of the literature indicated divergent views as to the proper parameters it seemed that several combinations of parameters should be investigated. Because of the enormity of the task, it appeared that the regression analyses for a variety of prediction formulae could best be performed by an electronic digital computer such as the IBM 650.

A regression analysis program (RAP) is available for use with this computer (1,2). This program compares observed data with data obtained from various parameters. In general, the program begins with a table of data and a proposed regression equation. This equation can be of any form, such as the simple linear polynomial:

$$Yc = Ao + A_1X_1 + A_2X_2$$

Where Yc is the computed result, Ao, A_1 and A_2 are constants and X_1 and X_2 are independent variables. The computer performs a series of trial calculations of Yc and compares the deviation of these results with the observed value Yo for each case by summing the squares of the differences between observed and computed results. If this deviation,

$$\text{Deviation} = (Yo - Yc)^2,$$

1. From the departments of biophysics, medicine and biochemical research, Touro Infirmary and Tulane University, New Orleans.

2. Aided by a grant from the John A. Hartford Foundation.

is a minimum, the best correlation exists between observed or measured and computed or predicted values. By successive approximations, the computer will obtain a set of coefficients, Ao, A_1 and A_2, for the test equation which will minimize this deviation. The magnitude of each coefficient will reflect the relative importance of each variable in the regression equation.

A further feature of RAP is the computation of certain statistical quantities for the resultant regression equation. These quantities include the coefficient of correlation, standard deviation and the chi-squared value. The coefficient of correlation can have any value from -1 to $+1$, where zero indicates no correlation, -1 indicates perfect correlation about a line perpendicular to the regression line and $+1$ indicates perfect correlation about the regression line. Values between these extremes will indicate the degree of correlation. The standard deviation is a measure of the distribution about the mean; thus plus or minus one standard deviation includes two-thirds of the population. The chi-squared value is a measure of the "goodness of fit" of the measured data with the predicted values. A table of chi-squared values will give the probability of such distribution occurring by chance alone. The smaller the chi-squared value the higher the correlation and the lower the probability of chance distributional occurrence. For a given set of data and a specified test equation, the computer will establish the coefficients of the equation which will give the best correlation and will measure success by statistical analysis.

The form of the test equation can be changed and the entire procedure may be repeated. Comparisons of the statistical results will indicate the relative correlation attained with each form of test equation. The repetition of this computation is simplified in that the deck of data cards is unchanged and only one or two cards of the program deck need be changed to effect a change in the test equation.

One hundred and fifty-five normal subjects were studied and blood volume, plasma volume, height, weight, age and sex were recorded. (3). The blood and plasma volumes were measured by dilution technique using radioactive iodinated human serum albumin. The plasma volume (PV) was estimated from the radioactivity measurements on plasma and the blood volume (BV) similarly was estimated from radioactivity measurements on whole blood. The peripheral hematocrit was computed from the formula:

$$\text{Hct.} = \frac{\text{BV} - \text{PV}}{\text{BV}}$$

The blood volume measurement was then corrected for the difference in peripheral hematocrit and average body hematocrit by the formula:

$$\text{BV (corrected)} = \text{BV (measured)} \frac{(1 - \text{Hct})}{1 - \text{Hct} \times 0.91)}$$

The data from the 155 normal adult subjects were coded and punched on cards for data entry into the computer in the manner prescribed for the gen-

eral RAP program. The blood and plasma volumes as punched were the direct result of the dilution computation. A conversion was included in the basic RAP program to correct for the difference between peripheral hematocrit and body hematocrit. Since weight and height were recorded in pounds and inches, appropriate unit conversions were performed by the computer.

Three formulae are commonly used in an attempt to predict circulating blood volume, viz., the body mass, the surface area and the height cubed-body mass formulae.

Body Mass Formula—75 ml./K × Body Mass (K) showed such lack of correlation with this parameter alone that it has been abandoned as a prediction formula as reported elsewhere (3,4).

Surface Area Formula. The relation of blood volume (BV) to surface area (SA) has been described by Baker (4) and the suggested prediction formula is:

$$BV\ (\text{liters}) = 2.68\ (\text{liters/sq. m.})\ SA\ (\text{sq. m})$$

where surface area is computed by the formula of Du Bois. (5)

$$SA = 0.007184\ H^{0.725} \times M^{0.425} \qquad \text{Equation (1)}$$

Thus, the basic formula is:

$$BV = 0.01925\ H^{0.725} \times M^{0.425}$$

where BV is volume in liters, H is height in centimeters and M is body weight in kilograms. To permit complete freedom for coefficient selection by RAP the test equation for regression was used in the basic form of the two primary variables, height and weight, as,

$$BV\ (\text{computed}) = A_1 H^{0.725} M^{0.425} + A_0$$

where A0 is a constant which RAP will provide if needed. This constant will be needed if the line of correlation is not collinear with the regression line.

Data from 92 males and 63 females were separately subjected to the regression analysis program. The resulting equations are shown in Table 1. The coefficient of height and weight has changed slightly from the formulation of Baker and is slightly different for males and females. The greatest change occurred in the addition of a pure constant by the computer. It may be noted that the constant is large and is significantly different for males and females.

TABLE 1.

SURFACE AREA PREDICTION FORMULAE FOR BLOOD VOLUME USING HEIGHT AND WEIGHT

Formula	*Source*
$BV = 0.0193\ H^{0.725}\ M^{0.425}$	Baker (4)
$BV = 0.0236\ H^{0.725}\ M^{0.425} - 1.229$	Computer (Male)
$BV = 0.0248\ H^{0.725}\ M^{0.425} - 1.954$	Computer (Female)

Rewriting these formulae in terms of the Du Bois surface area computation, Equation 1, the value of 3.29 liters/square meter for males and 3.47 liters/sq. meter for females is derived as compared with the previous value of 2.68 liters/sq. meter (Table 2).

TABLE 2.

SURFACE AREA PREDICTION FORMULAE FOR BLOOD VOLUME, EXPRESSED AS SURFACE AREA

Formula	*Source*
$BV = 2.68 \times SA$	Baker (4)
$BV = 3.29 \times SA - 1.229$	Computer (Male)
$BV = 3.47 \times SA - 1.954$	Computer (Female)

Height cubed and Body Mass: This prediction formula proposed by Allen et. al., (6) is of the form:

$$BV \text{ (predicted)} = A_1H^3 + A_2M + Ao$$

Where H is the height in meters and M is the weight in kilograms.

This formula was submitted to the computer with our group of 93 males and 62 females. The resultant formulae are compared with their counterparts from the literature in Table 3. Changes are noted in the coefficients and the pure constant. From the magnitude of the coefficient it appears that height is less important in the new formulation than that of Allen but its significance still exceeds that of the weight. The magnitudes of these coefficients vary only slightly between male and female but as in the surface area formula, the pure constant shows considerable change with sex.

TABLE 3.

HEIGHT-CUBED BODY-MASS PREDICTION FORMULA

Formula	*Source*
$BV = 0.417\ H^3 + 0.0450\ M - 0.030$	Allen (6) (Male)
$BV = 0.414\ H^3 + 0.0328\ M - 0.030$	Allen (6) (Female)
$BV = 0.367\ H^3 + 0.0322\ M + 0.604$	Computer (Male)
$BV = 0.356\ H^3 + 0.0331\ M + 0.183$	Computer (Female)

In addition to the regression equation, RAP also gives a statistical analysis, comparing the prediction by the equation with the observed value (for blood volume). Some of the results are tabulated in Table 4 for the computed formulae. The values for the correlation coefficient indicate that good correlation was achieved in all cases with slightly better correlation for females than for males. This is supported by the values for the standard deviation about the mean. The tabulation of the sum of the squares of the difference between observed and computed values indicates the degree of success of the computer in making this value a minimum. The chi-squared values yield a probability of about one

TABLE 4

STATISTICAL DATA FOR COMPUTER DERIVED FORMULAE FROM RAP

	H^3—BM		*Surface Area*	
	Male	*Female*	*Male*	*Female*
Correlation Coefficient	0.784	0.871	0.780	0.864
Std. deviation	0.506	0.479	0.507	0.486
$\Sigma(Yo-Yc)^2$	22.75	13.76	23.15	14.37
Chi-Squared	4.61	3.58	4.67	3.65

in ten thousand that this is chance distribution. From the results of the statistical analysis of RAP, there is no significant difference in the degree of correlation between the computer-derived surface-area formula and the computer-derived height cubed-body mass formula. Values for the application of the T-test and the F-test (not tabulated) were also obtained from the statistical part of RAP; they were in agreement with the findings reported above.

Further study was made on the height cubed-body mass formula in which the power of the height was changed from 3.2 to 2.0 in steps of 0.2. The coefficients of height and weight and the pure constant changed for each of the derived regression equations. This was indicative of a change in the relative importance of the variables for the prediction. The statistical data from RAP indicated that any of the derived equations could serve equally well as the prediction formula. This suggested that the power of the height as applied in the prediction of blood volume is not critical.

An attempt was made to evaluate the correlation which might be obtained from biased populations. Males and females were divided into three weight groups namely, those whose body weight was within 10 per cent of ideal and those whose body weight was more than 10 per cent different from ideal. In all three groups the correlation was much poorer than that obtained with the group as a whole.

A special statistical program† was written for the computer to compare the prediction formulae from RAP with the prediction formulae from the literature or any other source. With this program any data can be subjected to any equation and equivalent statistical evaluation obtained. Standard deviation about the mean for the measured and computed data, coefficient or correlation,

†Details of this program are available upon request.

chi-squared and the standard error of estimate are computed. The surface area formula, the height-cubed body-mass formula of Allen and both of the computer-derived formulae were applied to our group and Allen's group. The results of this study showed that either of the computer-derived formulae predicted better than either of the other formulae on all of the data tested. Attempted correlation with 363 determinations on normal subjects recorded in the literature has been reported elsewhere. (3).

SUMMARY

A method is described for the application of the electronic digital computer to the correlation of biological data. This method has been applied to the correlation of sex, height and weight with blood volume in the normal human adult. A statistical analysis is described to evaluate the efficacy of correlation. The information obtained from this technique is of great import in the evaluation of biological data.

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JOURNAL OF NUCLEAR MEDICINE 3:100, 1962

Concomitant Radioisotopic and Radiographic Cerebral Arteriography: Preliminary Observations[1]

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INTRODUCTION

The development of the technique for regional perfusion of the head and neck by Woodhall (3, 4, 5) has resulted in the prefection of a radioactive scanning device which permits discrete unilateral detection of isotopic elements of the perfusate within the head. As a sequelae to this development, the use of this instrument during cerebral arteriography has been made.

METHOD

Patients having clinical indications for cerebral arteriography, that is, syndromes suggestive of brain tumors, cerebrovascular disease, epilepsy and extracranial vascular disease comprised the study group. To date, some 25 patients have been studied. The studies are performed in the X-Ray Department. Patients received premedication consisting of 125 mg of Seconal® and in some instances heavier sedation when necessary in less cooperative patients. Percutaneous common carotid arterial puncture is performed, using 1 per cent Procaine as local anesthesia. Eighteen-gauge short-beveled hypodermic needles or 17-gauge Touy needles are used depending upon whether antegrade or retrograde injections are made. When the problem concerns itself solely with an intracranial diagnostic problem, the antegrade placement of the needle is made. Vertebral arteriography may be obtained by retrograde injection of the right carotid artery with contrast media after the distal carotid has been compressed. Experience has suggested

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that retrograde placement of the needle is desirable in cases of carotid occlusive disease in the neck in order that plaques are less likely to be dislodged, thereby propagating an embolus into the cerebral circulation.

In all instances, the contrast media used is 50 Hypaque® (Sodium Acetrizoate). The injectible quantity varies from 8 cc to 20 cc. The patient is placed upon the x-ray table and the neck hyperextended and arterial puncture carried out. Standard stereoscopic anterior posterior roentgenograms and lateral roentgenograms are made during manual injection of the contrast media. The needle is attached to a three-way stop cock which in turn is connected to a glass-tipped 10 cc syringe or a 20 cc Luer-Lok syringe as the injection quantity varies. Between the anterior posterior and the lateral roentgenograms, the scanning device is positioned and an isotopic scan is made. A 0.25 cc volume of hippuric acid tagged with 20 microcuries of I-131 in a tuberculin syringe is connected to the free edge of the stop cock, injected and followed by a 5 cc flush of physiological saline through the third opening of the stop cock.

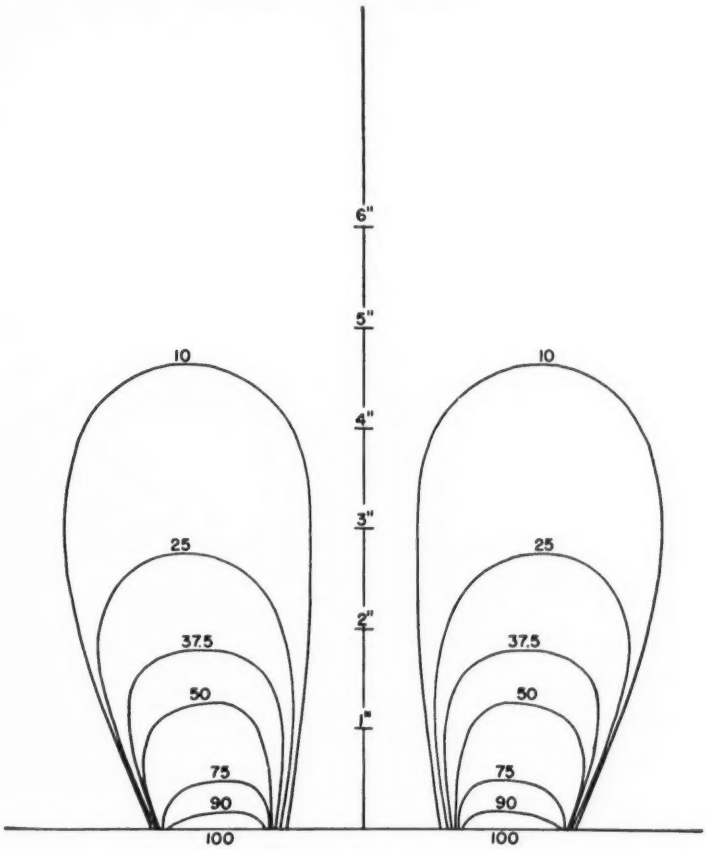

Fig. 1. Isoresponse curves, cerebral circulation probe

The radiation detection system incorporates two sodium iodide scintillation detectors mounted adjacent to each other in a single shield. The cone is positioned at the vertex of the skull in the coronal plane. The shield is constructed so that each detector is collimated to "see" only the volume straight ahead of the aperture. If a point source of radioactivity is moved along the midline between the two detectors, it is seen that the two detectors do not respond to its radioactivity until it is greater than six inches away from the face of the detectors along the midline (Fig. 1).

Each detector is connected to a count rate meter and then to a rectilinear strip chart recorder so that continuous activity levels are recorded before and after the injection of the radioactive material. The complete unit is seen in Figure 2.

Following completion of the injections, the needles are withdrawn and digital compression of the artery is made for several minutes to prevent hemorrhage.

RESULTS

A total of 25 patients were studied. Seventeen of the patients underwent bilateral arteriography. Of the total group, eight patients had the needle placed in a retrograde fashion. Twenty-one studies in this group were judged to be technically satisfactory. The four failures were attributed to technical malfunctioning of the recording equipment. Comparison of the arteriogram and isotopic flow-pattern graphs in light of the clinical findings were made. The anterior

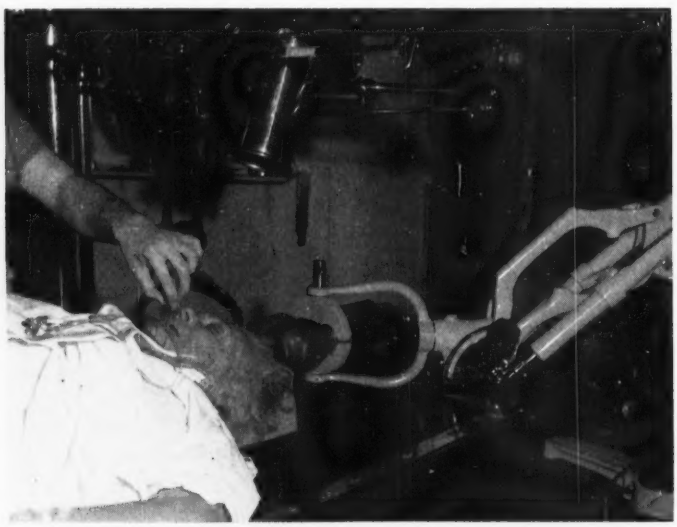

Figure 2. Photograph of patient on x-ray table with "flush" syringe in hand of operator, x-ray tube above head of patient, scintillation detector at vertex of skull leading to rectilinear strip chart recorder.

posterior roentgenogram was used in most instances for the comparison. The plotting of the isotopic curve as a function of time against concentration in what appears to be normal studies presents a sharp peak curve or slope, the ascending phase representing the arterial portion of the circulation in the descending portion of the graph representing the venous flow. The average duration of the cycle is approximately 12 seconds as measured by serial changing cerebral arteriography devices and an average of the isotopic curves. In cases of retrograde injection the appearance time is somewhat delayed and the take-off from the base line is somewhat elevated which would be expected inasmuch as the bolus must be forcefully injected into the blood stream and then carried "upstream" to reach the counting bed (Fig. 3). The base line may be lowered somewhat in retrograde injection by shielding of the syringe with lead. The "appearance time" is measured from the time of "starting" injection to the peak of the curve and the "disappearance time" is measured as the time required from the peak of the curve to reach the base line.

The flow patterns appear to correlate well with the arteriograms with regard to isolated or unilateral anterior cerebral artery filling from the injected side (Fig. 4). In some instances both anterior cerebrals fill from the same side and this is shown in Figure 3.

The concentration of isotope reaching the counting bed via the carotid injection does not appear to influence the flow patterns. In Figure 5, the flow graph shows the comparative curves of 20 microcuries of irradiation activity contained in a 0.25 cc volume and 100 microcuries in a 7.5 cc volume respectively.

The comparative flow graphs with internal and external carotid artery injections are noted in Figure 6. Instead of the usual peaked curve with internal carotid injections, a lower protracted curve is obtained with external injection.

Figure 7, is a study in a patient who had a clinically proven left extracranial internal carotid thrombosis three years prior to this study. Evidence of right brain ischemia precipitated the current study which consisted of a right retrograde common carotid injection. The arteriogram shows comparable anterior and middle cerebral filling on both sides, however, the isotopic flow pattern shows a higher concentration on the left side as compared to the right or injected side. The lower curve on the right side may be indicative of collateral flow occlusion.

Patients studied to date having brain tumors visualized on arteriograms have shown an abnormal flow graph pattern. Figure 8, shows a patient having a recurrent dural sarcoma. Abnormal tumor vessels are seen on the arteriogram with extension across to the left side. This compares with the graph which shows filling to some extent on the left side and a curve that is higher and more protracted than usual on the right side.

Arteriovenous malformations may show flow curves similar to tumor curves. One patient (Figs. 9, 10, 11) presented with signs of subarachnoid hemorrhage and right brain involvement. Figure 9, shows a high peaked curve of longer

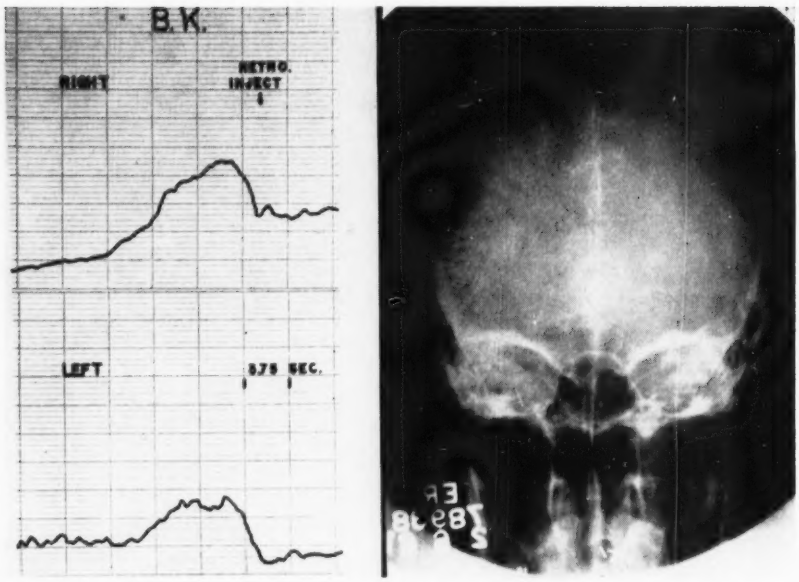

Figure 3. Isotopic flow graph with accompanying arteriogram of a patient with a venous hemangioma at the tongue. Retrograde injection into the right carotid showing high take-off baseline. There is bilateral anterior cerebral artery filling on arteriogram which compares with flow graph on left.

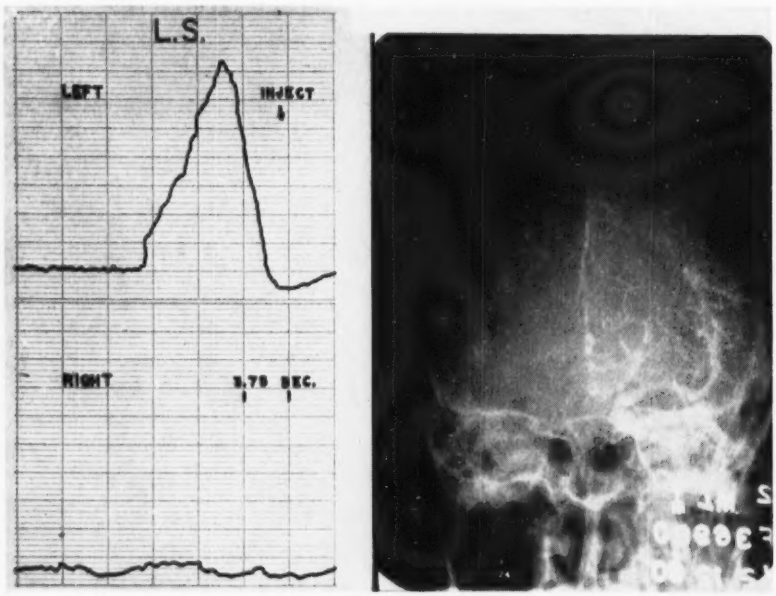

Figure 4. Left carotid injection showing unilateral anterior cerebral filling and unilateral flow graph.

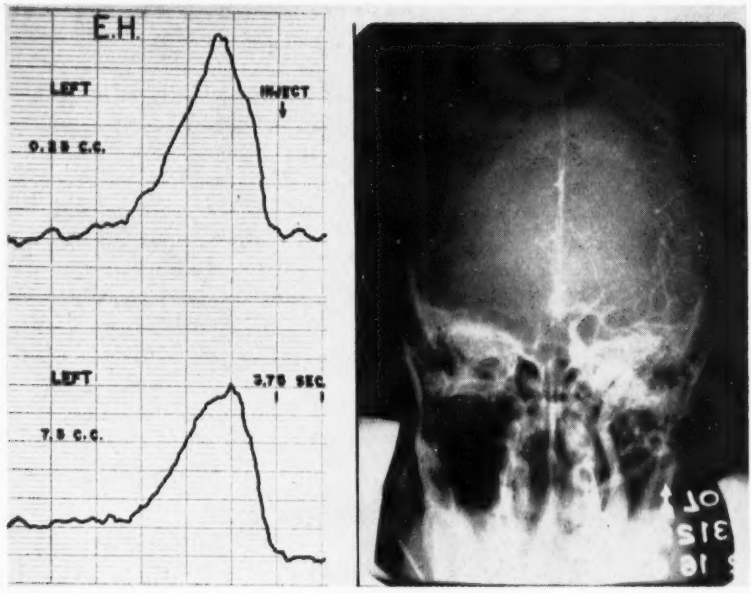

Figure 5. Left carotid injection of 20 microcuries of activity in 0.25 cc volume (upper) and 100 microcuries of activity in 7.5 cc volume (lower). The flow graph patterns are similar.

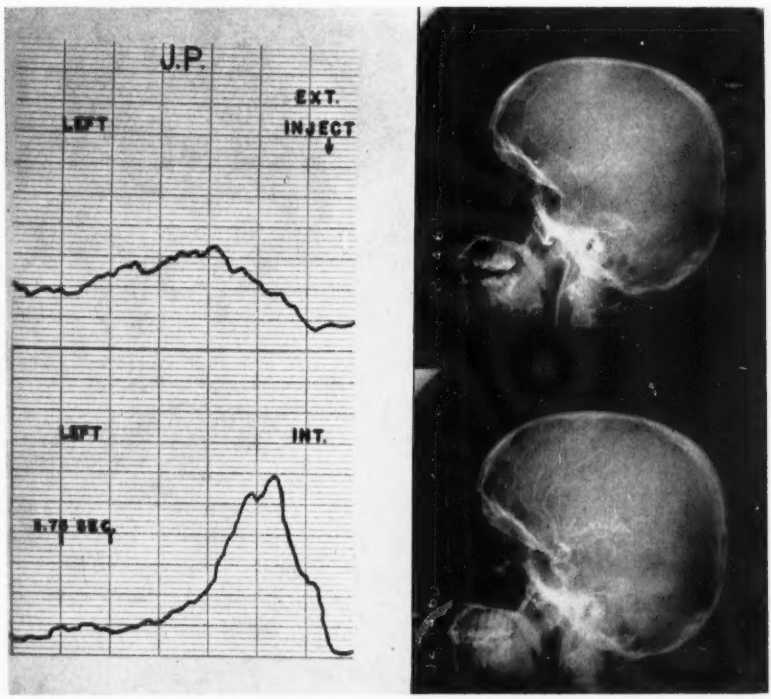

Figure 6. Left carotid injection into external carotid system (upper) and internal carotid (lower). The external injection flow graph is less peaked and represents a more protracted curve.

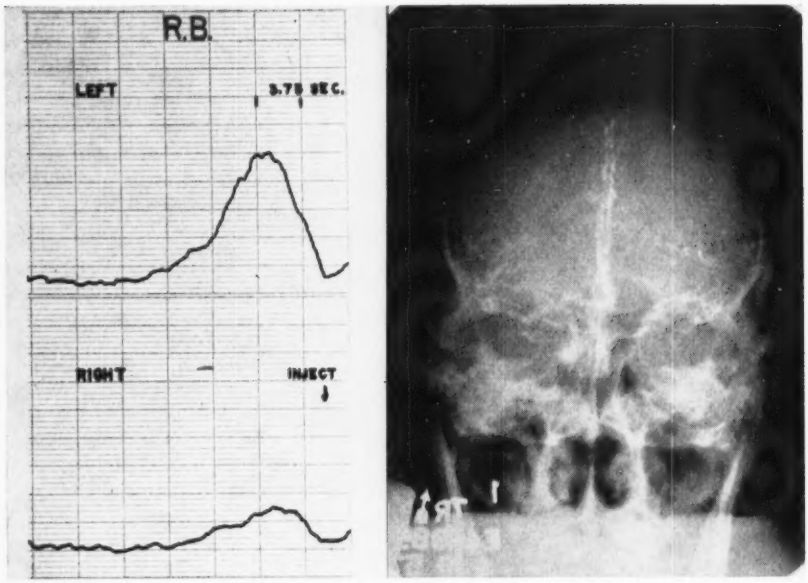

Figure 7. Right carotid injection in a patient with long standing left carotid artery occlusion in neck secondary to arteriosclerosis. Note complete filling of the cerebral vessels in the arteriogram, however, the flow graph shows greater flow on the left side of the brain.

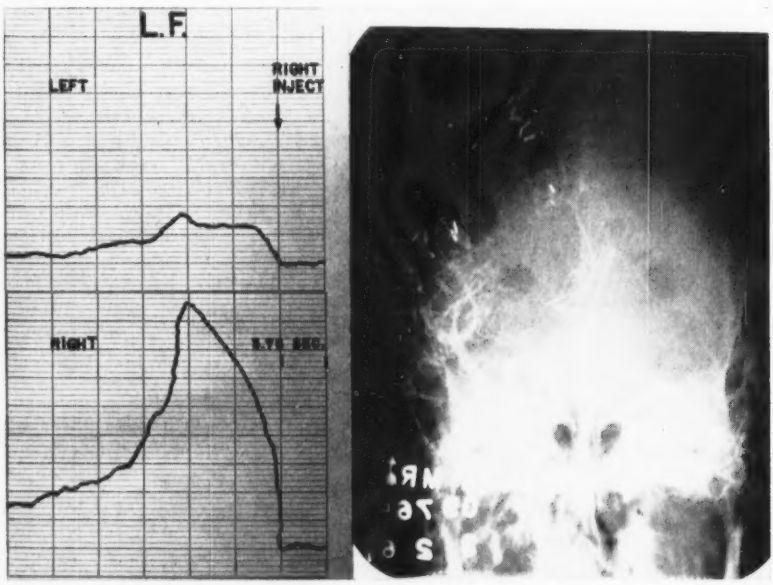

Figure 8. Right injection in a patient with recurrent dural sarcoma. There is a shift of the anterior cerebral artery from right to left and high peaked protracted flow graph on right side with some appearance on left side.

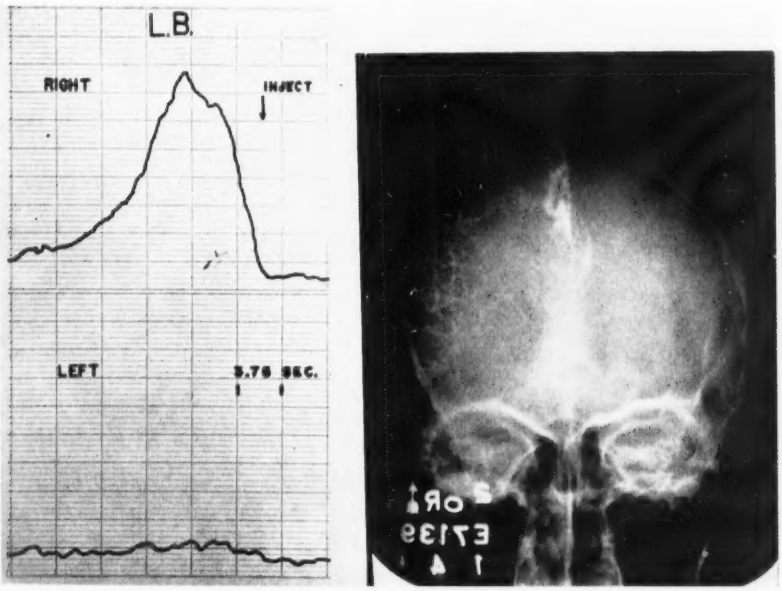

Figure 9. Right carotid injection in a patient with vascular malformation in the right parietal region. Note high peaked protracted flow graph which corresponds to collection of contrast material in midline on the arteriogram.

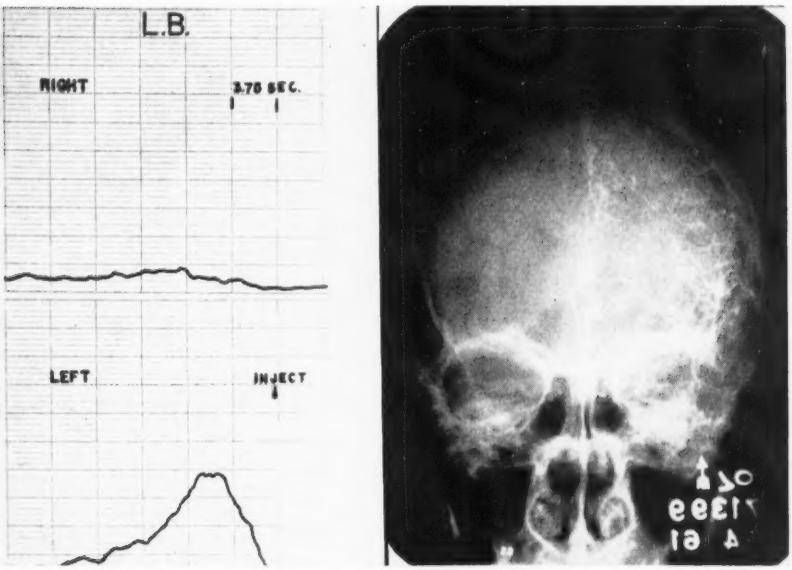

Figure 10. Same patient as Figure 9, with left injection. Unilateral arteriogram and flow graph filling is seen.

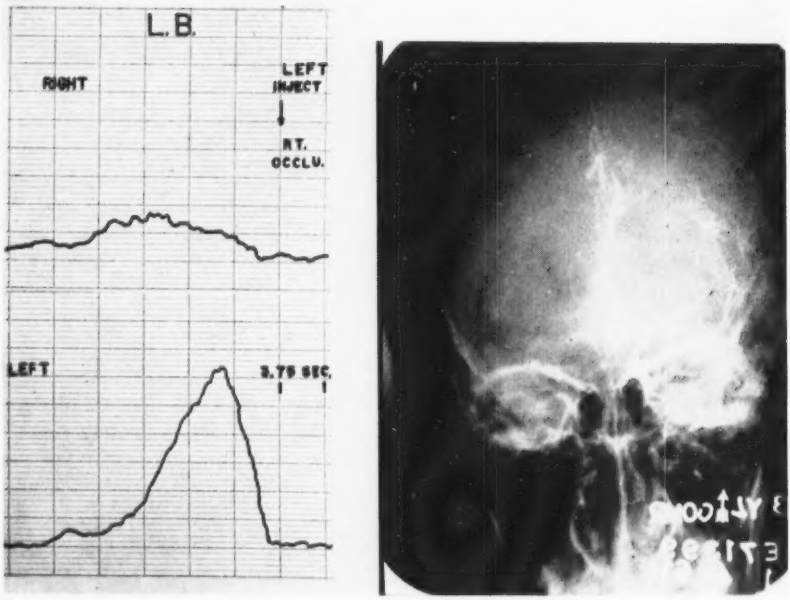

Figure 11. Same patient as Figure 9, with left carotid injection and simultaneous right carotid occlusion in the neck. Note slight filling of malformation near midline and appearance on flow graph (upper).

duration than usual and a unilateral flow pattern. The arteriogram demonstrates a malformation near the midline and posteriorly. Figure 10, in comparison to Figure 9, shows a unilateral left-sided filling pattern without cross-over. Figure 11, shows cross-over from left to right when the left carotid is injected and the right side digitally occluded in the neck. It would appear that the protracted curve of low intensity on the right side compares with the malformation as visualized on the arteriogram in the same figure.

COMMENT

It appears that qualitative flow patterns within the cerebrum can be obtained when small quantities as low as 20 microcuries of radioactivity are placed in the perfusate of the cerebral circulation. Nylin (1), with a complex apparatus, has measured cerebral blood flow using radioactive tagged erythrocytes. He has shown that in cerebrovascular disease plotted dilution curves differ from normal control cases and appear abnormal even when arteriograms fail to disclose an abnormality.

Oldendorf and Crandall (2), have suggested that cerebral blood flow patterns can be demonstrated with the intravenous injections of 400 microcuries of Hippuran. Investigation of this technique, using I-131 tagged Hypuric Acid injected into an antecubital vein, is currently being performed. This adjunctive

test may prove to be of value in those patients in which extracranial vascular disease is suspected and as a result of their vascular difficulties present themselves as poor risk candidates for percutaneous carotid arteriography.

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ANNOUNCEMENT

Applications for Fellowships in Clinical Investigation beginning July 1, 1962 are now being received at the Medical Division of the Oak Ridge Institute of Nuclear Studies. The Program includes the basic course in radioisotopes, and clinical training in the use of radioisotopes as tracer and therapeutic agents. The research program offers opportunities in radiation effects, hematology, thyroid disease, and cancer. Applications and information are available from Ralph M. Kniseley, M.D., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.

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Erythrocyte and Iron-Kinetics in Patients[1] With Chronic Pulmonary Emphysema

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INTRODUCTION

Low arterial oxygen saturation is associated with an increase in red cell volume, hematocrit, and hemoglobin concentration. This increase of erythrocyte values is found in persons living at high altitudes (1, 2, 3) with increase of erythropoiesis directly proportional to the degree of oxygen unsaturation. Similar changes are present in patients with anoxia resulting from primary hypoventilation (4, 5, 6, 7) or disturbed function of the respiratory center (8). Hypoxia in patients with pulmonary emphysema, however, does not usually provoke a similar increase of red cell volume, hematocrit and hemoglobin (1, 9, 10, 11, 12, 13). Furthermore, low hemoglobin concentration is usually found even when the hematocrit and red cell volume do correspond to the level of arterial oxygen saturation (12, 14, 15, 16).

It is not known why the erythrocyte response to hypoxia in pulmonary emphysema differs from that observed at high altitudes and in pulmonary hypoventilation. The problem was investigated in this study by quantitative measurement of erythrocyte kinetics using the iron-kinetic technique and model of Pollycove and Mortimer (17). In this way we can observe not only iron turnover, bone marrow activity and splenic sequestration and destruction of erythrocytes when present, but also the rate of plasma iron deposition in storage form, the amount of iron in the erythropoietic labile pool, daily hemoglobin synthesis, mean erythron life span and mean effective erythron hemoglobinization time (Fig. 1).

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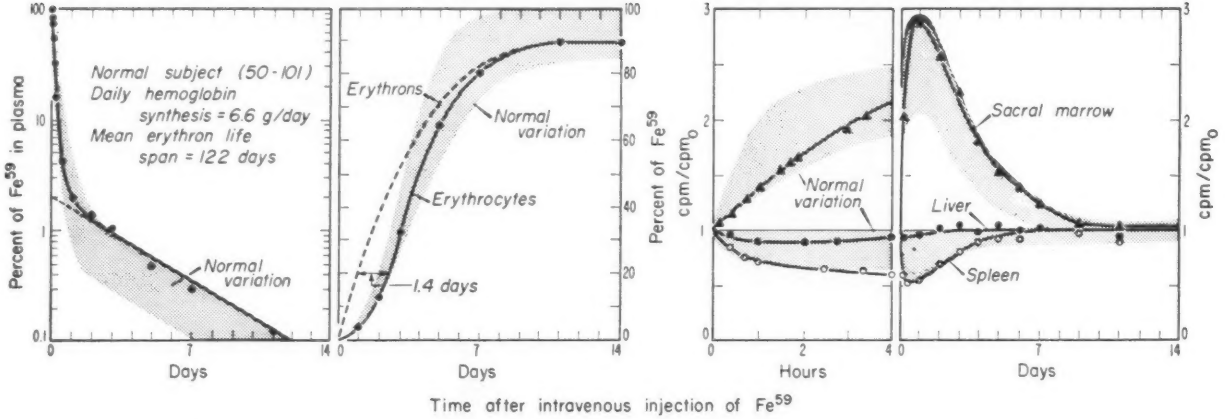

Fig. 1. (Normal subject) A 31 year old man, weight 70 kg. On the left is shown the decrease of radioiron in plasma following a single intravenous injection. Two different constant rates of radioiron leaving plasma are observed signifying re-entry of radioiron into plasma. Measurements of the two slopes, intercept C, and total plasma iron are used to determine that of 36 mg of iron leaving plasma daily, 23 mg is fixed in maturing erythrons. This corresponds to daily synthesis of 6.6 gm hemoglobin. Relating this rate of hemoglobin synthesis to constant total body hemoglobin, a mean erythron life span of 122 days is obtained. The net incorporation of radioiron in circulating erythrocytes and marrow erythrons (dotted curve) is shown next. The mean time required for iron to pass through the marrow into the circulation is called mean hemoglobinization time and normally is 1.0-1.8 days. On the right is shown the body radioiron distribution occuring in the first few hours and in the following 14 days. Initial accumulation of Fe^{59} occurs only in the marrow—subsequently marrow release is complete at the 8th to 9th day, corresponding to the appearance of radioiron in circulating erythrocytes.

MATERIALS AND METHODS

Fifteen patients with chronic pulmonary emphysema were studied, two female and thirteen male. Ages varied from 40 to 80 years. The diagnosis was established by clinical evaluation and respiratory function tests. Arterial oxygen saturation was measured with the technique of Van Slyke and Neill (18). Emphysematous patients with varying degrees of arterial oxygen desaturation were selected, two of them being at a borderline low normal of oxygen saturation. Bone marrow aspiration was performed for observation of cytology and hemosiderin deposition. Measurements of hemoglobin concentration, hematocrit, red cell count, reticulocyte count, white cell count and platelet count were made on venous blood. Erythrocyte sedimentation rate (Wintrobe tube) was included in the study. Observation pertinent to detection of infection are presented in Table I. Red cell volume was determined at the beginning and again at the end of the iron-kinetic study, with P^{32} labeled erythrocytes; plasma volume was determined using Fe^{59} labeled β_1-globulin. Plasma iron concentration and latent iron binding capacity were determined by the method of Peters et al. (19). The iron-kinetic study was developed using the technique of Pollycove (17, 20).

RESULTS

Polycythemia was found in six patients (Tables 2 and 3, Fig. 2, patients

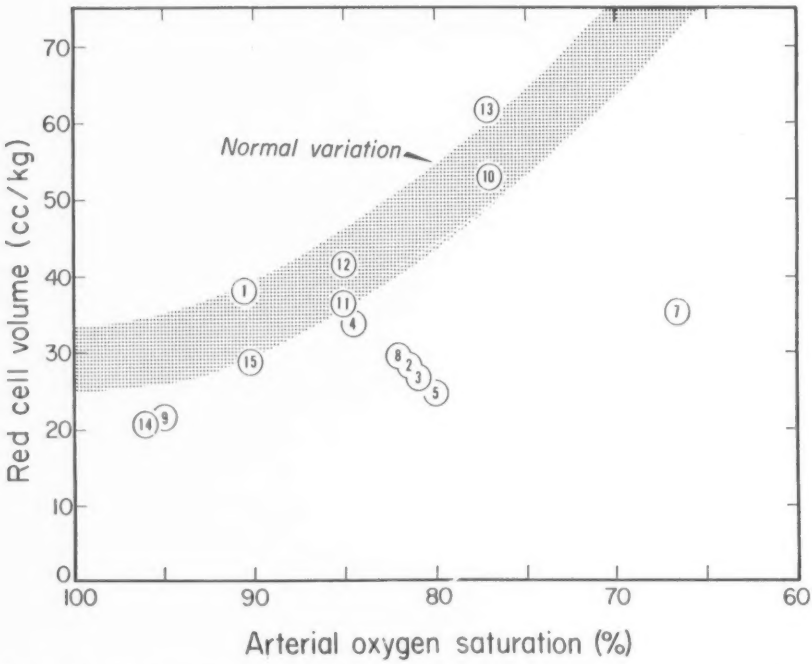

Fig. 2. Red cell volume values are plotted along the ordinate vs. arterial oxygen saturation values along the abscissa. The normal variation was constructed with the results reported by Lawrence (3a).

TABLE 1.

Patient	Fever	Increased Sed. Rate	Purulent Sputum	Pathogenic Bacteria	X-ray Suggesting Pneumonitis	Leukocytosis	MARROW: Myeloid Hyperplasia	MARROW: Hemosiderin	Remarks
Emphysema									
10. C.H.	0	—	0	—	0	0	0	—	
11. I.G.	0	—	0	—	—	0	0	—	
12. H.H.	0	—	0	—	0	0	—	—	
Emphysema with Infection									
1. V.B.	+	—	+	—	+	0	—	—	
3. Joe M.	+	+	+	—	+	+	+	++	
4. L.F.	+	0	—	—	—	+	0	0	Iron deficiency also present
5. Jim M.	+	+	+	0	+	+	0	+	
6. J.G.	+	+	+	+	—	0	0	0	Iron deficiency also present
7. C.S.	+	+	+	+	+	+	—	—	Sputum smear and culture + for TBC
9. R.G.	+	+	+	+	+	+	—	—	
13. W.C.	+	+	+	—	+	0	+	++	
14. W.S.	0	+	+	+	+	0	—	—	
15. P.R.	+	+	+	+	+	0	—	—	
Emphysema with Iron Deficiency									
8. Y.H.	0	—	0	—	0	0	0	0	
Emphysema with Possible Inflammation									
2. F.R.	+	0	0	—	0	0	—	—	

TABLE 2.

Patients	*Arterial Oxygen Saturation*	*Red Cell Volume ml./kg.*	*Plasma Volume ml./kg.*	*Blood Volume ml./kg.*	*Corrected Sedimentation Rate mm./hr.*	*Reticulocytes %*	*Hematocrit %*	*Hemoglobin gm./100 ml.*	*Mean Corpuscular Volume cubic micron*	*Mean Corpuscular Hemoglobin micromicrograms*	*Mean Corpuscular Hemoglobin Concentration %*
Normal Range:	96–100	24–33	32–45	56–78	0–15	0.3–1.3	37–54	12–18	82–92	27–31	32–36
Emphysema											
10. C.H.	77.0	52.7	32.4	85.1	—	0.8	67.5	16.9	95	23.9	25.0
11. I.G.	85.0	36.3	33.6	69.8	—	0.4	53.5	13.3	104	26.0	24.9
12. H.H.	85.0	41.3	37.3	78.6	—	0.6	55.0	17.4	94	29.9	31.6
	[a]82.3±4.6	43.4±8.4	34.4±2.5	77.8±7.7		0.6±0.2	58.7±7.7	15.9±2.2	97.7±4.5	26.6±3.0	27.2±3.8

[a]One standard deviation.

TABLE 2—*Continued*

Patients	*Arterial Oxygen Saturation*	*Red Cell Volume ml./kg.*	*Plasma Volume ml./kg.*	*Blood Volume ml./kg.*	*Corrected Sedimentation Rate mm./hr.*	*Reticulocytes %*	*Hematocrit %*	*Hemoglobin gm./100 ml.*	*Mean Corpuscular Volume cubic micron*	*Mean Corpuscular Hemoglobin micromicrograms*	*Mean Corpuscular Hemoglobin Concentration %*
Emphysema with Infection											
1. V.B.	90.6	38.4	62.0	100.4	—	0.5	48.0	12.4	105	27.0	25.8
3. Joe M.	81.0	26.8	58.7	85.5	29.0	0.4	44.5	14.0	95	29.9	31.4
4. L.F.	84.6	34.1	39.1	73.2	4.0	0.4	50.0	14.2	99	28.1	28.4
5. Jim M.	80.0	24.8	41.3	66.1	49.0	0.3	41.0	11.6	94	26.7	28.3
6. J.G.	—	20.4	44.4	64.8	40.0	0.6	38.0	9.7	102	26.0	25.5
7. C.S.	66.7	36.1	49.8	86.0	30.0	0.4	42.0	14.6	100	34.8	34.8
9. R.G.	95.0	21.4	41.1	62.5	47.0	0.6	38.5	11.7	111	33.6	30.3
13. W.C.	77.0	62.2	47.0	109.2	20.0	0.7	62.0	16.2	113	29.5	26.1
14. W.S.	96.0	20.3	39.2	59.5	51.0	0.4	39.0	11.2	97	27.9	28.7
15. P.R.	90.3	26.4	35.3	61.7	15.0	0.6	46.5	13.4	111	31.9	28.8
	84.6±8.9	31.1±12.1	45.8±8.3	76.9±10.8	31.7±15.5	0.5±0.1	45.0±6.9	12.9±1.8	102.7±6.4	29.5±2.9	28.8±2.7
Emphysema with Iron Deficiency											
8. Y.H.	82.0	29.7	58.7	88.4	—	0.5	41.0	10.6	98.1	25.3	25.9
Emphysema with Possible Inflammation											
2. F.R.	81.6	28.6	39.0	67.6	7.5	0.1	49.2	15.4	108.4	33.9	31.3

•One standard deviation.

1, 7, 10, 11, 12, 13). The diagnosis of polycythemia was based on increased red cell volume. All of these patients, with the exception of patient 7, responded with a normal increase of red cell volume to decreased arterial oxygen saturation (Fig. 2). Patients with uncomplicated secondary polycythemia show relatively normal iron-kinetics with erythropoiesis increased proportionately to increased red cell volume, erythron life span remaining normal (21, 22). This pattern was found in two of these patients (Table 3, Fig. 3, patients 10, 12). Patient 11 had decreased hemoglobin synthesis, possibly the result of improved oxygenation of arterial blood with therapy, with increased iron exchange between plasma and storage. This iron kinetic pattern is characterized by primary deposition of iron in the liver and by the presence of three exponential components in the removal of radioiron from plasma (Fig. 4) (20, 23). Hemoglobin synthesis was increased in patients 1 and 13 sufficiently to compensate for mild hemolysis in addition to maintaining the normal increase of red cell volume in response to hypoxia (Table 3, Fig. 5). Adidtional diagnosis of alcoholism and cirrhosis were established in patient 1. Chronic bronchial infection was present in patient 13 as evidenced by copious sputum, radiographic changes and elevated sedimentation rate. Patient 7 has superimposed acute infection, pneumonia, with considerable reduction of mean erythron life span (Table 3).

Infection or chronic inflammation was observed in 9 patients (3, 4, 5, 6, 7, 9, 13, 14, 15) as evidenced by some or all of the following signs and symptoms: malaise, fever, increased sedimentation rate, cough with purulent sputum, pathogenic bacteria, leukocytosis, radiographic changes suggesting pneumonitis, myeloid hyperplasia of the marrow, reduction of both plasma iron concentration and iron binding capacity, and normal or increased amounts of hemosiderin in marrow (Table 1). The iron-kinetic pattern of these patients is characterized by decreased plasma iron concentration and decreased total binding capacity of the plasma, slight to moderate increase of hemoglobin synthesis inadequate to compensate for reduction of mean erythron life span, absence of significant splenic sequestration and destruction of erythrocytes, and prolongation of mean hemoglobinization time (Fig. 6) (21, 24).

Iron deficiency was present in patient 8 with decreased plasma iron concentration, increased total plasma iron binding capacity and absence of bone marrow hemosiderin. The iron kinetic pattern is similar to that present in those patients with infection except that total plasma iron binding capacity is increased rather than decreased (20, 23).

Patient 2 had erythropoiesis increased sufficiently to maintain a normal red cell volume despite moderate shortening of erythron life span. In this respect erythrocyte kinetics was similar to the above mentioned patients with infection but differed in that plasma iron concentration and total binding capacity were normal and no evidence of infection except intermittent fever was found at the time of study; a history of alcoholism and frequent recurrent previous infections was present.

Erythrocyte mean corpuscular volume was increased in the patients studied (Table 2). Similar findings have been demonstrated by other investigators and shown to be a result of hypoxia (8, 13, 16).

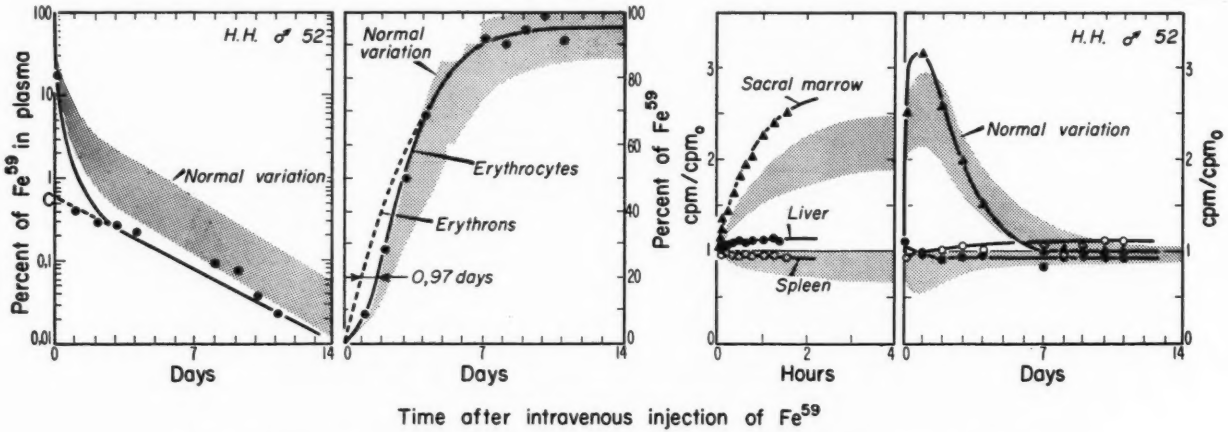

Fig. 3. (Patient 12) A 52 year old man; weight 78.2 kg; hemoglobin 17.4 g/100 ml. Measurements of both slopes of radioiron leaving the plasma, intercept C, and total plasma iron are used to determine that of 49.3 mg iron leaving plasma daily 28.2 mg is fixed in the erythron. This corresponds to daily synthesis of 8.29 gm hemoglobin, 1.34 gm per liter of blood (normal 1.0-1.6 gm/1/d). Relating this rate of synthesis to constant body hemoglobin 1073 gm., a mean erythrocyte life span of 129 days is obtained. Maximum incorporation of radioiron into circulating erythrocytes is 95% (normal 85-100%). *In vivo* measurements show that there is rapid uptake of radioiron in the bone marrow. Subsequently marrow release is normal without secondary accumulating of iron in spleen or liver. The hemoglobinization time is at the lower limit of normal, 0.97 days (normal 1.0-1.8 days).

TABLE 3.

Patients	*Arterial Oxygen Saturation %*	*Plasma Fe Concentration γ/100 ml.*	*Total Fe Binding Capacity γ/100 ml.*	*Plasma Fe Turnover mg./h/1*	*Net Incorp Fe^{59} in Circ. Erythrocytes per cent*	*Fe for Hemoglobin Synthesis mg./h/1*	*Hemoglobin Synthesis gm./day/1*	*Mean Erythron Life Span—days*	*Mean Erythron Hemoglobinization Time—days*
Normal Range: (12 subjects)	96–100	70–170	300–400	0.22–0.40	85–100	0.14–0.33	1.0–1.6	102–132	1.0–1.8
Emphysema									
10. C.H.	77.0	270	—	0.39	88	0.24	1.6	122	1.8
11. I.G.	85.0	150	—	0.21	85	0.11	0.65	135	1.4
12. H.H.	85.0	54	400	0.33	95	0.19	1.34	129	1.0
	[a]82.3±4.6	158±108	400	0.31±0.09	89±5	0.18±0.07	1.2±0.5	129±7	1.4±0.4

TABLE 3—*Continued.*

Patients	*Arterial Oxygen Saturation %*	*Plasma Fe Concentration γ/100 ml.*	*Total Fe Binding Capacity γ/100 ml.*	*Plasma Fe Turnover mg./h/1*	*Net Incorp Fe^{59} in Circ. Erythrocytes per cent*	*Fe for Hemoglobin Synthesis mg./h/1*	*Hemoglobin Synthesis gm./day/1*	*Mean Erythron Life Span—days*	*Mean Erythron Hemoglobinization Time—days*
Emphysema with Infection									
1. V.B.	90.6	147	323	0.31	74	0.24	1.69	58	2.7
3. Joe M.	81.0	54	216	0.36	72	0.27	1.90	52	3.7
4. L.F.	84.6	23	245	0.23	88	0.22	1.53	87	2.9
5. Jim M.	80.0	52	152	0.27	70	0.26	1.80	62	3.0
6. J.G.	—	12	234	0.25	78	0.22	1.52	50	3.2
7. C.S.	66.7	182	424	0.56	70	0.53	3.74	29	3.9
9. R.G.	95.0	30	219	0.18	69	0.16	1.15	90	2.5
13. W.C.	77.0	325	343	0.33	68	0.25	1.78	71	3.7
14. W.S.	96.0	87	262	0.22	90	0.21	1.47	71	3.6
15. P.R.	90.3	107	353	0.28	85	0.26	1.85	72	3.7
	84.6±8.9	102±91	277±77	0.30±0.10	76±8	0.26±0.09	1.84±0.67	64±18	3.3±0.6
Emphysema with Iron Deficiency									
8. Y.H.	82.0	25	425	0.21	94	0.20	1.43	62	2.8
Emphysema with Possible Inflammation									
2. F.R.	81.6	164	322	0.33	84	0.31	2.15	72	2.3

*One standard deviation.

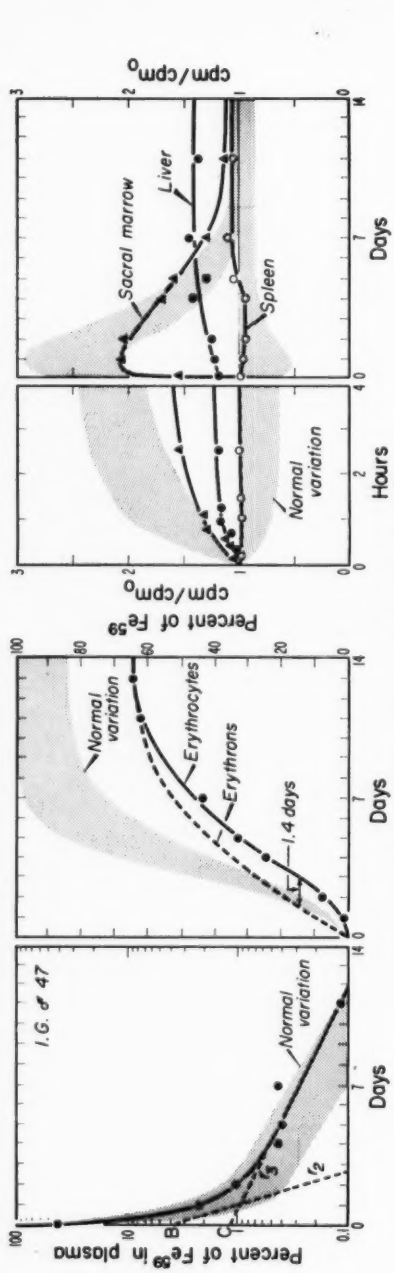

Fig. 4. (Patient 11) A 47 year old man; weight 79.6 kg; hemoglobin 12.8 g/100 ml. Three different constant exponential rates of radioiron leaving the plasma are present. The presence of three rates suggests that iron re-enters in plasma from two different labile pools. Measurements of the three slopes and intercepts B and C, incorporation of radioiron into erythrons and total plasma iron are used to determine that of 17.8 mg iron leaving plasma daily 12.6 mg is fixed in marrow erythrons. This corresponds to daily synthesis of 3.7 gm hemoglobin, 0.67 gm per liter of blood (normal 1.0-1.6 gm/l/d). Relating this rate of synthesis to decreasing total body hemoglobin 767 gm. a mean erythron life span of 135 days is obtained (normal 102-132 d).

Maximum net incorporation of Fe^{59} in red cells is 65% (normal 85-100%). This value is lower than normal as a result of plasma iron deposition in storage. *In vivo* measurements show iron leaving the plasma after injection accumulates in both bone marrow and liver. Subsequently, marrow release is normal and storage deposition continues until the 4th day. Splenic sequestration of circulating erythrocyte does not occur during the period of study. The mean erythron hemoglobinization time of 1.4 is normal (1.0-1.8 d).

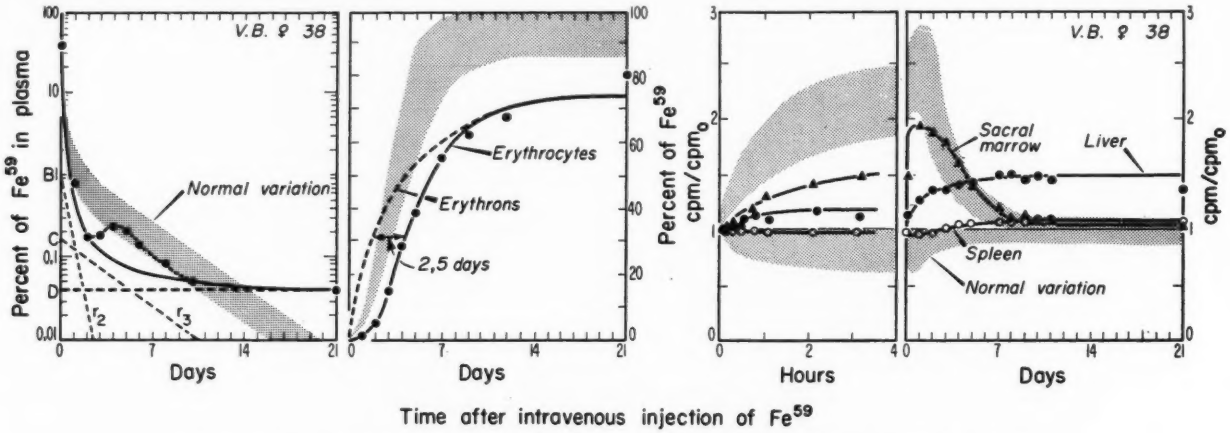

Fig. 5. (Patient 1) A 37 year old woman; weight 42.7 kg; hemoglobin 12.4 mg/100 ml. Three different constant exponential rates of radioiron leaving plasma are present. The dotted curve shows the transient modification of the plasma radioiron due to the hemolysis. Continued re-entry of radioiron into plasma from hemolyzed red cells results in a stable equilibrium level, D. The presence of three exponential rates suggests that iron re-enters plasma from two different labile pools. Measurements to the three slopes and intercepts B and C, incorporation of the radioiron into the erythrons, and total plasma iron are used to determine that of 31.6 mg iron leaving plasma daily, 24.4 mg is fixed in marrow erythrons. This corresponds to daily synthesis of 7.2 gm hemoglobin, 1.68 gm per liter of blood (normal 1.0-1.6 gm/l/d). Relating this rate of synthesis to constant total body hemoglobin 416 gm a mean erythron life span of 58 days is obtained (normal 102-132 d). Maximum net incorporation of Fe^{59} in the red cells is 75% (normal 85-100%). This value is lower than normal as a result of both increased plasma iron deposition in storage and mild hemolysis. *In vivo* measurements show iron leaving the plasma after injection accumulates in both bone marrow and liver. Subsequently, marrow release is delayed and storage deposition continues until the 5th day. Splenic sequestration of circulating erythrocytes does not occur during the period of study. The mean erythron hemoglobinization time of 2.7 days is prolonged (normal 1.0-1.8 d).

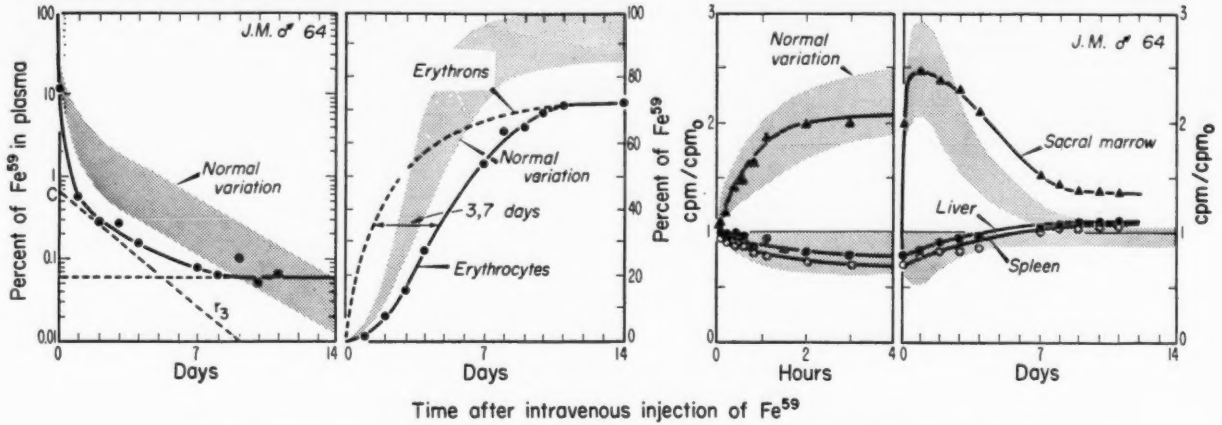

Fig. 6. (Patient 3) A 64 year old man; weight 47.3 kg.; hemoglobin 14.3 gm/100 ml. Measurements of both slopes of radioiron leaving the plasma, intercept C, and total plasma iron are used to determine that of 34.8 mg iron leaving the plasma daily, 26.4 mg. is fixed in erythrons. This corresponds to daily hemoglobin synthesis of 7.8 gm. Relating this rate of hemoglobin synthesis to the constant total body hemoglobin of 405 gm., a mean erythron life span of 52 days is obtained (normal 102-132 d). The maximum net incorporation of Fe^{59} into circulating erythrocytes is only 72% (normal 85-100%). This reduction of erythrocyte radioiron incorporation is a result of hemolysis. *In vivo* measurements show normal accumulation of Fe^{59} in bone marrow without other primary deposition. Subsequently, marrow release is markedly delayed with a corresponding increase of mean erythron hemoglobizination time of 3.7 days (normal 1.0-1.8 d). These findings indicate marrow destruction of erythrons. No splenic sequestration of erythrocytes is observed.

DISCUSSION

The degree of polycythemia, as measured by increased red cell volume, was in normal proportion to the degree of hypoxia in emphysematous patients without superimposed infection, inflammation, or iron deficiency (Fig. 2, patients 10, 11, 12). When these complications were present, red cell volume was decreased in 3 patients (patients 6, 9, 14), within normal range for individuals without hypoxia in 4 patients (patients 3, 5, 8, 15), increased slightly with subnormal response to hypoxia in 2 patients (patients 4, 7), and increased normally in 2 patients (patients 1, 13, Fig. 2). Mean erythron life span was normal in emphysematous patients without complications and reduced in all patients with complications (Table 3). Reduction of erythron life span was generally slight to moderate, being considerable in only one patient in whom there was a recent onset of pneumonia (patient 7).

Patient 2, with arterial oxygen saturation of 82 per cent, showed no increase of red cell volume and mean erythron life span was shortened to 72 days. This patient was not iron deficient and did not show any overt sign of infection except intermittent fever, despite a history of alcoholism and numerous recurrent bronchial infections.

Though red cell volume increased in normal proportion to hypoxia in 5 patients (Fig. 2) and hematocrit so increased in 7 (Fig. 7), a similar increase of

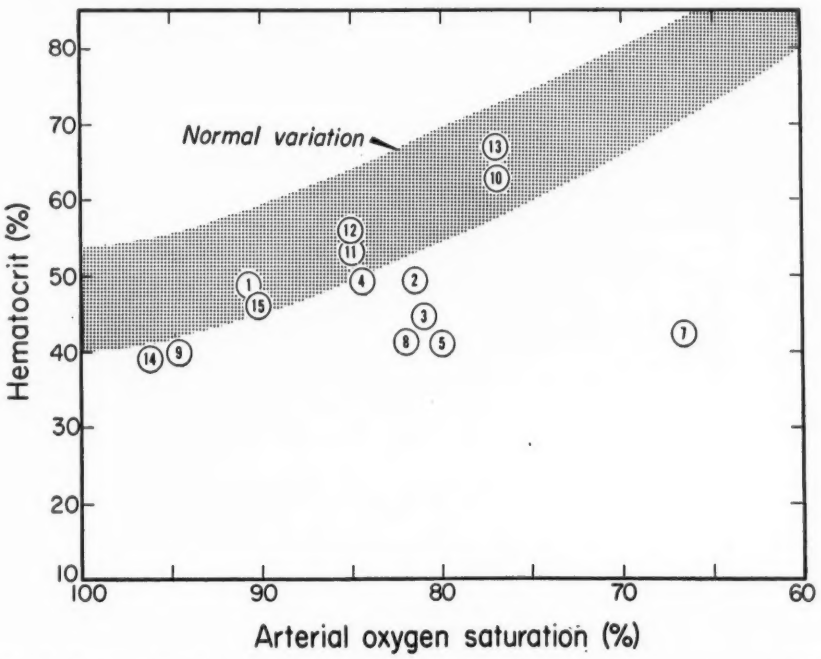

Fig. 7. Hematocrit values are plotted along the ordinate vs. arterial oxygen saturation values along the abscissa. The normal variation was constructed with the results reported by Hurtado et al. (1).

hemoglobin concentration was observed in only 1 patient (patient 12, Fig. 8). A decrease of erythrocyte hemoglobin concentration is expected in iron deficiency (patient 8) and in patients with infections in whom plasma iron concentration is characteristically subnormal (patients 3, 4, 5, 6, 9). Three polycythemic patients (patients 1, 10, 11), however, had normal or increased plasma iron concentration, yet there was no increase of blood hemoglobin concentration in response to severe or moderate hypoxia. Decreased mean corpuscular hemoglobin concentration was also observed in emphysematous patients by Gelpi et al. (15), Hammersten et al. (14), and Grant et al. (16). Grant et al (16) explained this observation to be a result of the measured inverse ratio between erythrocyte water and hemoglobin concentration. It seems unlikely that active increase of erythrocyte water produces a decrease of erythrocyte hemoglobin concentration. Probably a primary decrease of hemoglobin in red cells permits a corresponding increase of cell water. Low erythrocyte hemoglobin concentration may be due to different rates of adaptation of erythrocyte production, and hemoglobin synthesis to the decrease of arterial oxygen saturation. This interpretation could be supported by the results of Linman et al. (25) who reported an ether soluble, heat stable erythropoietic plasma factor stimulating erythroblastic proliferation. When this material was injected into rats an erythrocytosis was observed without increase of hematocrit or hemoglobin concentration. The direct effect of hypoxia

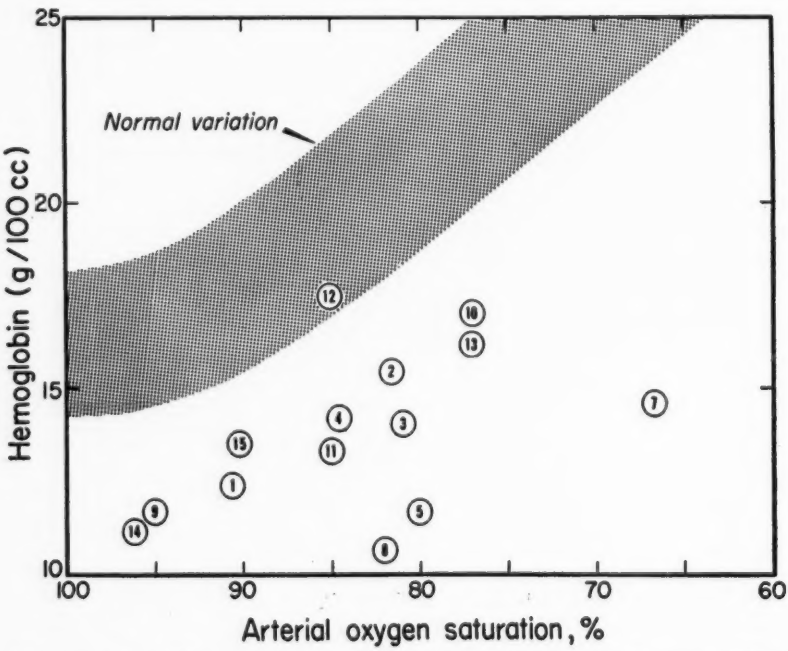

Fig. 8. Hemoglobin values are plotted along the ordinate vs. arterial oxygen saturation values along the abscissa. The normal variation was constructed with the results reported by Hurtado et al. (1)

on erythropoietic tissue observed *in vitro* is characterized by decreased proliferation, cellular degeneration (26, 27) and decreased heme synthesis (28). In some cases low hemoglobin concentration in blood can be related to increase of plasma volume, as in patients 1, 3, 8. These observations are not sufficient to explain our findings of low blood and erythrocyte hemoglobin concentration because Hurtado et al (1) observed normal erythrocyte hemoglobin concentrations in polycythemic individuals with chronic high altitude hypoxia and arterial oxygen saturations as low as 62 per cent. With extreme hypoxia, however, mean corpuscular hemoglobin concentration was decreased, averaging 30 per cent (normal 32-36 per cent) in 5 subjects with arterial oxygen saturation of 43-59 per cent.

Plasma iron concentration was increased (patient 10) or at a high normal level (patient 11) in patients with uncomplicated emphysema. The plasma iron concentration of patient 12, also without complication, was decreased as a result of venesection 5 days before study. Patients 1 and 2 had high normal and patients 7 and 13 had higher than normal concentrations of iron in plasma despite infection or inflammation. This increase of the plasma iron concentration may be partially the result of increased intestinal absorption of iron consequent to hypoxia, as observed in rats by Vassar and Taylor (29) and Krants et al (30).

Increased red cell destruction in patients with infection or inflammation also contributes toward a high concentration of iron in plasma.

Hemolysis in emphysematous patients was observed by Gelpi et al (15) by measuring mean erythrocyte life span with Cr^{51} labeled erythrocytes. Similar results were obtained in our patients when pulmonary emphysema was complicated by infection, inflammation or iron deficiency. We would like to emphasize, however, that much of the hemolysis probably occurs in bone marrow. The radioiron technique used in this study measures erythron survival from the moment iron is fixed in immature erythrons. In this way it is possible to demonstrate the hemolytic process in marrow by measuring mean effective erythron hemoglobinization time. The prolongation of this time signifies either a slowing of red cell maturation or destruction of maturing erythrons with reincorporation of radioiron. The early persistent feedback of iron into plasma when erythron hemoglobinization time is polonged and the shortened mean *erythron* life span as compared with mean circulating erythrocyte life span as measured with CR^{51} or DFP^{32} suggest bone marrow hemolysis rather than slowed red cell maturation (20, 23, 31).

SUMMARY

The degree of polycythemia, as measured by increased red cell volume, was in normal proportion to the degree of hypoxia in emphysematous patients without superimposed infection, inflammation, or iron deficiency. These complications, however, were present in most of the emphysematous patients studied and a subnormal response to hypoxia usually occurred.

Mean erythron life span was normal in emphysematous patients without complications and reduced in all patients with superimposed infection, inflammation or iron deficiency. Reduction of erythron life span was generally slight to moderate, much of this hemolysis probably occurring in bone marrow.

Erythrocyte mean corpuscular volume was increased in these patients, probably as a result of hypoxia.

Erythrocyte mean corpuscular hemoglobin concentration was decreased in these patients. This finding could not be shown to be the result of either low serum iron concentration or hypoxia *per se*.

Plasma iron concentration was generally increased in these patients with emphysema, probably as a result of increased red cell destruction and increased iron absorption secondary to hypoxia.

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ERRATUM:

In the article "Myocardial Scanning with Rubidium-86" in the January 1962 issue of this journal, Figures 1a and 1b were inadvertently transposed. The figure printed on Page 82 should appear above the legend for Figure 1a and the figure printed on Page 81 should appear above the legend for Figure 1b.

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Multicrystal Large Well Counters[1]

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INTRODUCTION

In one extreme, high sensitivity gamma counters which depend upon absorbing with good geometry a large solid angle of the emitted radiation, are available as small sample-volume well counters. In the other extreme, high sensitivity total body counters have been developed. In the intermediate range attempts are being made to explore such devices as the "ham" (1) counter, as well as liquid and plastic good geometry counters for laboratory animals. It appeared that some biological and medical research high sensitivity counting problems could be solved in this intermediate range (20 ml sample to several liters sample volume) by using irregular pieces of thallium activated sodium iodide which are immersed in a suitable fluid and arranged in an approximately two inch thickness around the space containing the sample. This contrasts with a ten inch thickness of plastic scintillator in the "ham counter". As the two inch of crystal will absorb more than half of the most penetrating gamma rays and much more than half below about .3 mev, in most applications, it is unnecessary to have a greater thickness than this. Thus it is possible to gain several distinct practical advantages over the use of plastic and liquid scintillators. First, the overall weight and size of the shield can be made a minimum. Second, average light path lengths between a scintillation and a photomultiplier photocathode can be kept shorter, thereby cutting down optical absorption light losses. Alternatively, fewer photomultiplier tubes would be needed. Third, the scintillations in the sodium iodide are considerably brighter than those from a liquid or plastic. Fourth, a much higher ratio of photoelectric absorption and practically simultaneous reabsorption of Compton scattered quanta is obtained.

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1. From the Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California at Los Angeles. These studies were supported by contract AT(04-1)GEN-12 between the Atomic Energy Commission and the University of California.

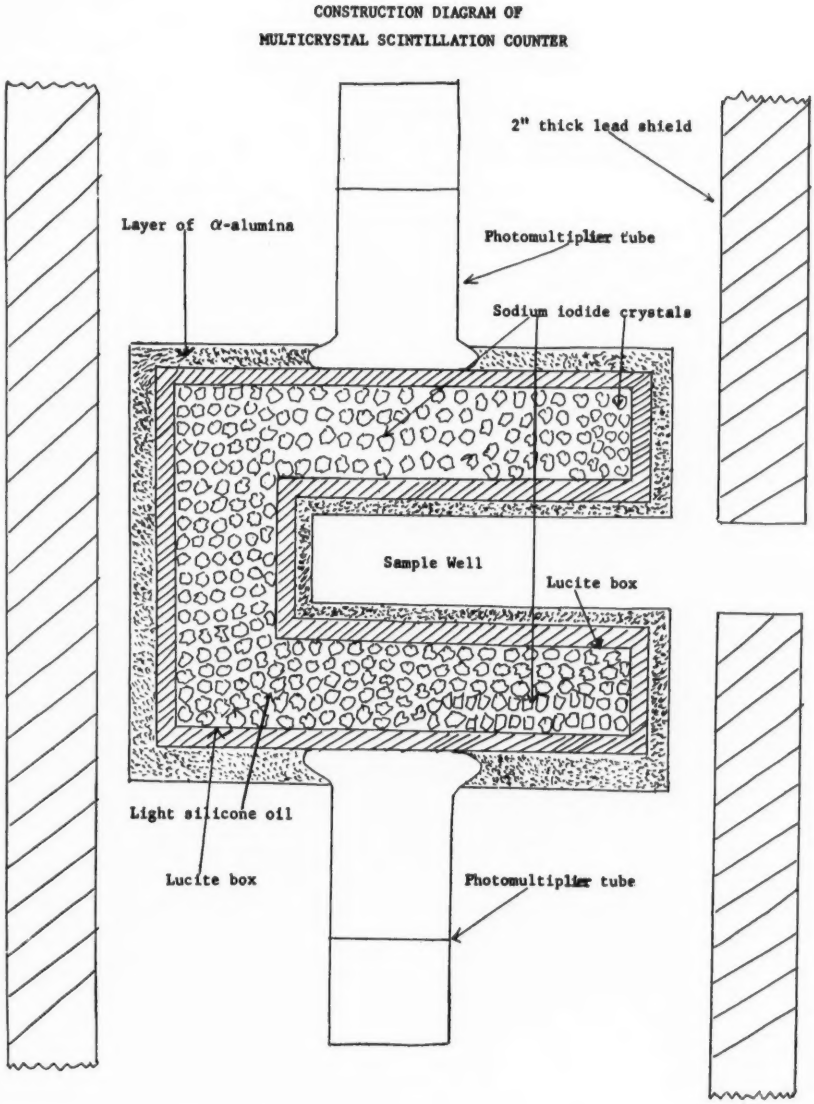

Figure 1. Diagrammatic Section of Multicrystal Counter

Even in a single crystal the average light path from a scintillation to absorption in the photosensitive surface of the photomultiplier tube or tubes statistically involve many diffuse reflections from the white coating applied to the surface of the crystal. It was reasoned that if the crystals were in pieces immersed in a suitably optically clear fluid, fairly efficient optical pathways could still be maintained. An additional relatively finite number of reflections and refractions would exist in most light paths at the crystal-fluid interfaces. Ideally it would be preferable to have a fluid that matched the refractive index of the crystals (refractive index 1.77). Practically no such fluid exists without a high dispersion and strong absorption in the near ultraviolet where part of the emission of the scintillations occurs. This absorption also occurs in Arochlor oil which has about the highest refractive index (about 1.63) of any ordinary chemically inert clear fluid. It was reasoned on the basis of the aforementioned lack of absorption during refraction and reflection that a low refractive index fluid should be satisfactory. A light silicone fluid is now being used. It was realized later that if immersed crystals had too high a degree of symmetry in their shape, theoretically, permanently trapped light paths could exist due to total internal reflection. The effect of such light entrapment would be to cause a spread of pulse heights for a single quantum energy, depending on where the scintillations occurred. However, the scintillations are bright enough that even partial escapement of light will produce a well-defined pulse.

A critical factor determining the range of application of multicrystal counters is the cost of the sodium iodide pieces. The cost apparently now depends on the supply and demand situation on trimmings from large single crystals. If demand were sufficient, it is likely that large scale production of the smaller pieces could enable the price to be lowered considerably.

CONSTRUCTION

Unexpected practical difficulties were encountered in building the first model of a multicrystal counter. It was built to count 20 to 30 ml blood samples or tissue samples. Progress on it was reported at the 1959 Chicago Meeting of the Society of Nuclear Medicine. Since then the difficulties were gradually solved and a new model was constructed to hold 120 ml. This model works very well and is in almost continuous use. Fig. 1 shows diagrammatically the construction of the new model. About 10 Kg of irregular crystal pieces of sodium iodide are packed in a lucite box (Figs. 2 and 3) with a re-entrant well. The voids are filled with a low viscosity silicone oil. A few small scrapings of metallic sodium are added as a vigorous dehydrating and deoxidizing agent.

A loose fitting thin metal shield surrounds the box, leaving a space approximately ⅛ inch. A layer of dry, finely powdered α-aluminum oxide is packed in this space. A loose fitting thin aluminum tube is placed in the well, the space outside of it also is packed with the white powder. Two opposing five inch photomultiplier tubes are used, one above and one below applied to plane faces of the lucite box. Of course, the reflecting powder is packed as close to the phototube

face as possible without interfering with light reaching the active phototube face. The phototubes are electrically in parallel so that their simultaneous pulses add.

The whole assembly is placed in a two inch thick lead shield (Fig. 4). The shield is mounted on a portable stand (as shown in Fig. 5).

PERFORMANCE

When the photomultipliers are operated at the plate voltage giving a pseudo-plateau on the counts per sec versus plate voltage semilog plot, the background

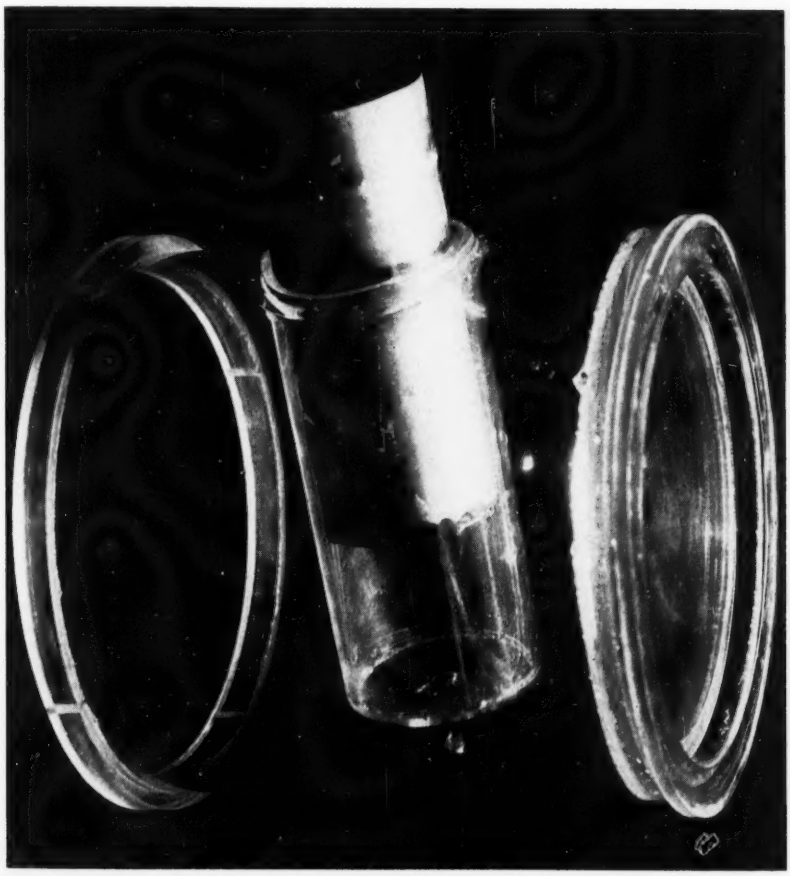

Figure 2. Multicrystal Counter
Lucite container before filling.
Inside diameter—5-3/4 in.
Inside length—6-1/2 in.
Outside diameter of well—2-1/8 in.

count varies from 40 to 50 counts per second. To illustrate a typical test with I^{131}, a sample calibrated independently as being .00596 microcuries took 1322 seconds to give 256,000 gross counts. The gross count rate was 193.7 c/sec. With a measured background of 43 c/sec (based on 256,000 counts over about 6000 sec or 1 hr and 40 min), the net count rate is 151 c/sec. The absolute disintegration rate of .00596 microcuries is .00596 × 37,000 = 221 d/sec. The absolute efficiency of counting this sample is then 151/221 = 68.3%. Tests with 'calibrated' mock iodine sources appear to give efficiences from 70 to 80%.

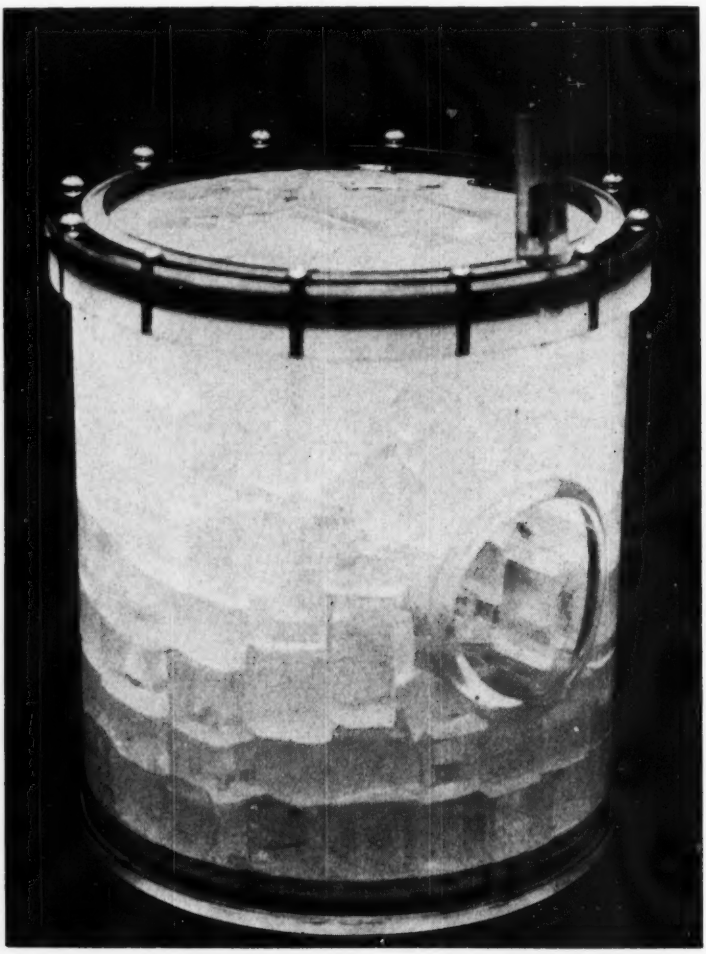

Figure 3. Lucite Container Filled with Pieces of Sodium Iodide Crystals. The voids are filled with a light silicone oil.

Figure 4. Lead Shield and Mobile Support

Extensive aliquot dilution tests show that the net count is linear from 2×10^{-5} microcuries of I^{131} to 0.2 microcuries. More than 0.2 microcuries could not be counted satisfactorily. By linearly extrapolating the net count rate of the above sample of I^{131} to obtain a net equal to background, it turns out that the gross count of a sample of .0017 mirocuries of I^{131} would double the background. If the counter is perfectly stable during the counting time for 256,000 counts, the statistical accuracy is $\pm$ .2% when the count rate is many times background. At a gross count rate of twice background as in counting .0017 microcuries, the statistical accuracy is $\pm$ .49%. For .00017 microcuries it would be $\pm$ 3% involving about 1¾ hrs. counting time.

Higher energy emitters above 1 mev appear to give absolute efficiencies around 50 to 60 per cent. When Co^{60} disintegrates two quanta 1.17 and 1.33 mev are emitted simultaneously as far as the resolution of the counter is concerned. When a scintillation crystal subtends only a small solid angle to the source it is probable that when one of these quanta is absorbed the other escapes. However, in a thick enough crystal assembly intercepting a large solid angle the probability of absorbing both quanta simultaneously becomes appreciable. The proportion of 2.5 mev summation pulses thereby increases.

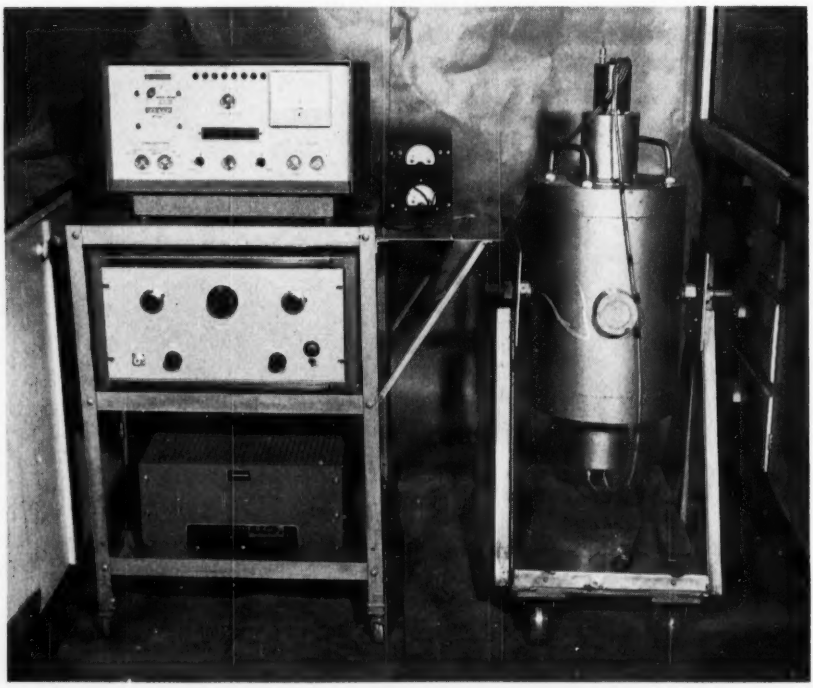

Figure 5. Multicrystal Counter Appearance of Complete assembly with scaler, spectrometer and voltage regulator.

It was hoped that this counter would show reasonably good spectrometric performance. This has not been realized to date but efforts are being made to determine the basic reasons for failure and whether or not they can be ameliorated. It appears that one cause of light loss on some pulses is that the scintillations occur inside of too symmetrically shaped crystal pieces and that some of the light is trapped by total internal reflection in very long light paths, until it is absorbed by the small optical absorption of the sodium iodide. Tests are under way to see if destroying cubic symmetry of cleaved pieces of NaI will increase the optical and radiospectrometric efficiency.

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Isotope Studies For The Evaluation of Venous Disease of The Lower Extremity[1,2]

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INTRODUCTION

In 1927 Blumgart and Weiss (3) presented a method using radioisotopes for the measurement of the velocity of blood flow in man. They injected an active deposit of radium C into the antecubital vein of one arm and detected its time of arrival in the other arm by means of a modified gas cloud chamber device (7). Extensive studies were carried out on normals as well as a number of patients with cardiovascular (4) and pulmonary disease (5). In 1948 Wright and his associates (8, 9, 10, 11) employed a direct method for measuring the rate of venous blood flow in the lower extremities (foot-groin flow time) with radioactive isotopes ($Na^{24}Cl$ in isotonic saline). They found alterations occurring in the rate of flow following changes in position and temperature. In further studies they demonstrated that pregnancy, labor, ascites and abdominal tumors slowed the venous return from the lower limbs. Recently, Zankel et al (12) used intravenous isotope injections with a single scintillation detector over the sapheno-femoral junction to evaluate the effect of physical methods for speeding up the venous circulation.

Recent reports from this department (1, 2) on the use of various laboratory tests for the evaluation of post-phlebitic disease briefly described the use of venous isotope studies. This test was designed for three main purposes: 1. to determine the extent of deep venous involvement, 2. to distinguish between primary varicose veins and post-phlebitic incompetent superficial collaterals, 3. to evalaute the efficacy of the present surgical management of the latter condition and its complications. Further evaluation of this technique was subse-

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quently carried out on a large number of patients including four clinical groups, viz., normals, post-phlebitic disease, primary varicose veins, and patients with vena caval ligations. An analysis of the tracings and an interpretation of the results as well as the clinical application of this test will be discussed.

MATERIALS AND METHODS

Table 1 lists 13 studies carried out on 84 patients. The normals were selected at random from the public surgical service at Duke Hospital; this group included general and thoracic surgical patients without clinical history of lower limb disorders (traumatic, osseous, muscular, or vascular). The patients studied with post-phelbitic disease, primary varicose veins, and vena caval ligations were selected from the surgical service at Duke Hospital and from the Durham Veterans Administration Hospital. One patient with a lymphangiomatous malformation of the lower extremity was examined. No cases studied have been excluded.

Technique of Venous Isotope Studies

Figure 1 is a sketch illustrating the most satisfactory technique in our experience for venous isotope outflow studies. Bilateral rubber-tube tourniquets were placed above the ankles after the legs were dependent for three to five minutes. The patient was then placed in a supine position with his knees slightly flexed. The dorsalis pedis vein or a suitable tributary was chosen for venapuncture. The legs were then extended and simultaneously recording scintillation detectors were placed over the knee (popliteal vein), in the inguinal

TABLE 1

EXAMINATIONS IN VENOUS ISOTOPE STUDIES

Type	*Number*
Normals	84
Post-phlebitic disease	44
Primary varicose veins	14
Inferior vena cava ligation	10
Vascular malformations	1
Total	153

region (sapheno-femoral junction), and to the right of the umbilicus (inferior vena cava). In patients with vena caval ligation, the third detector was placed below and to the right of the xyphoid process. Care was taken to place the detectors so that none were moved by abdominal respiratory excursions.

Five microcuries of I^{131} in approximately 0.5 ml of radioactive diodrast were injected as a bolus using a tuberculin syringe and a No. 24 needle. Bending the needle to a 150° angle at the neck facilitated puncture of the small vessel. When blood entered the syringe, the recording counters were started. The tourniquet was released and the injection completed promptly. The site of injection was then massaged slowly and gently. Care was taken to avoid subcutaneous injection of the radioactive material or to incite undue anxiety. If

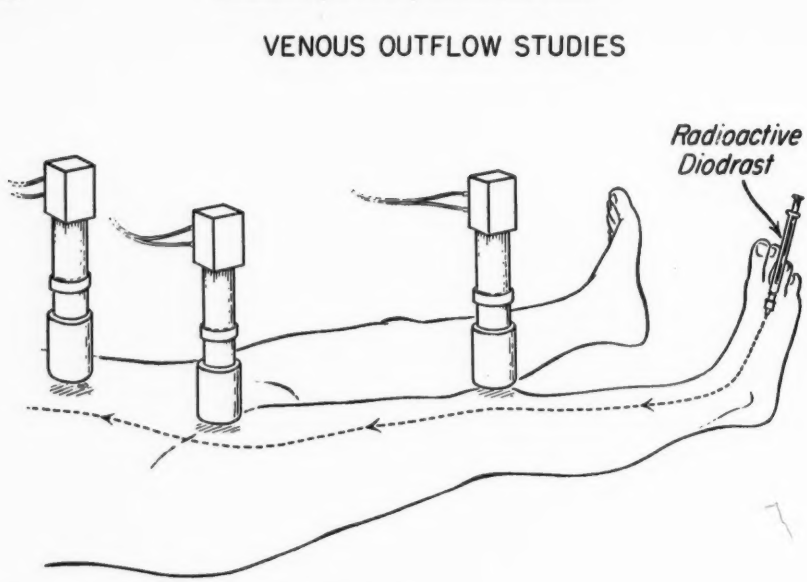

Figure 1. Technique for venous isotope studies.

this occurred the results were vitiated and the study was repeated later.

In cases of post-phlebitic incompetent superficial collaterals and in primary varicose veins the test was done with and without supporting elastic bandages whenever possible.

RESULTS

Normal Tracing

The isotope tracing had three components, viz., a latent interval from the time of injection to the onset of the rise, the rise to its maximum elevation (the wave), and the return to base-line level (Fig. 2). The latent interval represented the circulation time and only background counts were recorded. In the normal the circulation time was a function of the physiologic status of the particular venous system examined. The wave of radioactivity was traced by the number of impulses imparted by the column of radioactive material in the vessel passing beneath the scintillation counter. In the normal individuals the wave), and the return to base-line level (Fig. 2). The latent interval repretively undispersed material arrived at the recording station. The height of the wave and the sustained level reached varied directly with the amount of isotope injected, i.e., the magnitude of the wave depended solely on the concentration of the radioactive material beneath the counter. The declining segment of the curve (return to base-line) was always more gradual than the rise. This latter observation was presumably due to a number of concomitant phenomena, viz., dilution and dispersion of the radioactive matertal in the venous blood and the return of the material in the associated arterial vessels.

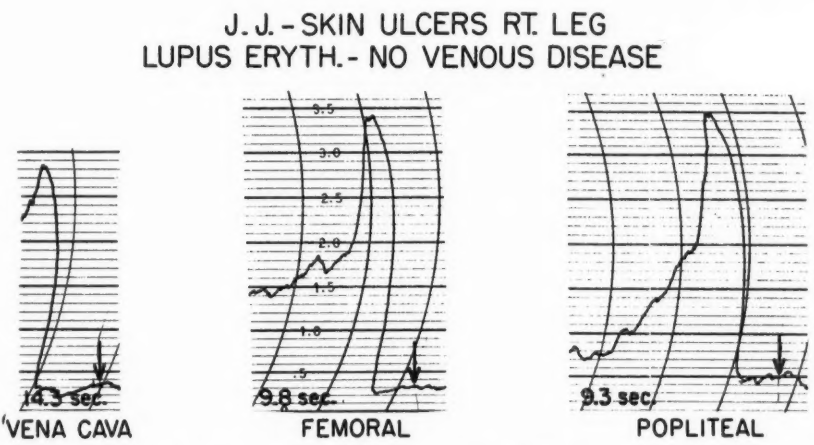

Figure 2. A normal isotope outflow study in a patient without venous disease. The arrow indicates the time of injection. The time listed in seconds is the lag period between injection and the perception of radioactivty at each counter.

Abnormal Tracing

In the diseased venous system the wave of radioactivity was latered both in height and the extent of the sustained elevation prior to return to the base-line level (Fig. 3). A delayed column of radioactive material dispersed by numerous and tortuous channels resulted in a slow, jagged, irregular rise in the wave of radioactivity. This wave rise was to a lower level, was sustained for a longer period of time than in the normal, and returned to the base-line after some delay. The rate of fall was dependent upon the extent to which the column of radioactive material was dispersed, and the degree to which the radioactive material was diluted by blood flowing into it from tributary veins as it passed up the limb.

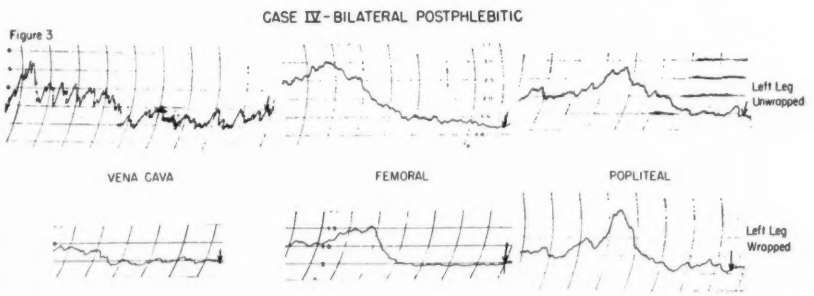

Figure 3. Abnormal venous isotope outflow study in a patient with bilateral post-phlebitic involvement of the lower extremities. Wrapping the leg with elastic bandages improved the flow of the isotope.

Angles of Radioactivity and Circulation Times

The slope of the wave of radioactivity, i.e., the angle subtended by the tangent to the curve (and to the horizontal on Esterline-Angus tracing paper) of radioactivity at each recording site appears to be a significant measure of abnormal physiology. It will be referred to as the tracing angle. In normals, it usually was clearly defined with average vaules of approximately 90°-100° at the popliteal, at the femoral, and the vena cava counters (Fig. 2). Table 2 tabulates the average circulation times in 84 normal controls.

TABLE 2

AVERAGE CIRCULATION TIMES IN 84 PATIENTS

	Circulation Time (seconds)
Popliteal Counter	
Injection to rise	10.8
Rise	15.3
Femoral Counter	
Injection to rise	18.6
Rise	21.8
Vena Cava Counter	
Injection to rise	19.6
Rise	42.4

Table 3 shows the average circulation times and tracing angles in studies of patient with post-phlebitis disease of the lower extremities, primarily varicose veins, and ligation of the inferior vena cava. The average circulation time of patients with post-phlebitic disease without supporting bandages was slightly longer than when wearing elastic supports, while both were longer than the normal average. The average circulation time of patients with varicose veins was slightly longer than the normals. When patients wore elastic supports, this time was shortened.

The average tracing angle in patients with thrombo-phlebitic involvement was greater in patients without supporting elastic bandages, while the latter approximated the normal. The average angle in patients with primary varicose veins wearing elastic stockings was less than those without support. The latter group closely and more uniformly approximated the normal than did the post-phlebitics.

The average circulation time of patients with ligation of the inferior vena cava approximated the normal range, while the tracing angle at each counter appeared very much the same as the normal.

Clinical Applications

The practical application of this examination may be illustrated in the following cases.

Case 1. A patient with refractory pretibial ulceration of his right leg had normal circulation times and angles of radioactivity (Fig. 2). This suggested that the deep venous system was not involved and that ulceration was not due to repeated inflammatory change with stasis. A diagnosis of discoid lupus erythematosis was subsequently made, and the ulcers healed uneventfully on conservative management.

TABLE 3

AVERAGE CIRCULATION TIMES AND ISOTOPE TRACING ANGLES IN VENOUS ISOTOPE STUDIES

	Circulation Time (secs) with bandages	*Circulation Time (secs) without bandages*	*Angle with bandages*	*Angle without bandages*
A. Post-phlebitic Disease				
Popliteal				
Injection to rise	11.6	12.4		
Rise	18.2	23.6	117°	123°
Femoral				
Injection to rise	19.3	21.4		
Rise	28.4	32.8	120°	134°
Inferior Vena Cava				
Injection to rise	29.2	33.0		
Rise	64.3	69.5	143°	153°
B. Primary Varicose Veins				
Popliteal				
Injection to rise	10.1	12.2		
Rise	22.9	28.9	132°	138°
Femoral				
Injection to rise	18.1	22.9		
Rise	27.8	35.7	136°	142°
Inferior Vena Cava				
Injection to rise	24.9	42.1		
Rise	35.8	48.2	138°	146°
C. Ligation of inferior vena cava				
Popliteal				
Injection to rise	10.5			
Rise	16.3		111°	
Femoral				
Injection to rise	17.3			
Rise	28.3		121°	
Inferior Vena Cava				
Injection to rise	25.8			
Rise	69.3		145°	

Case 2. A young man with a recent episode of pain and swelling in the calf of the right leg was admitted with a clinical diagnosis of acute thrombophlebitis. This was substantiated by the isotope studies, viz., an increased circulation time but a somewhat normal wave of radioactivity with and without elastic supports (Fig. 6).

Case 3. A seven year old boy with marked and prolonged enlargement of the right lower extremity was admitted with the diagnosis of lymphedema. He had compensatory orthopedic deformities of the hips, spine, and legs. The isotope studies revealed a normal circulation time and angles of radioactivity, and thereby discarded any suggestion of venous involvement which was substantiated by venography. At subsequent operation, an extensive lymphangiomatous malformation of the entire extremity was found to be the cause of the marked hypertrophy of the limb (Fig. 7).

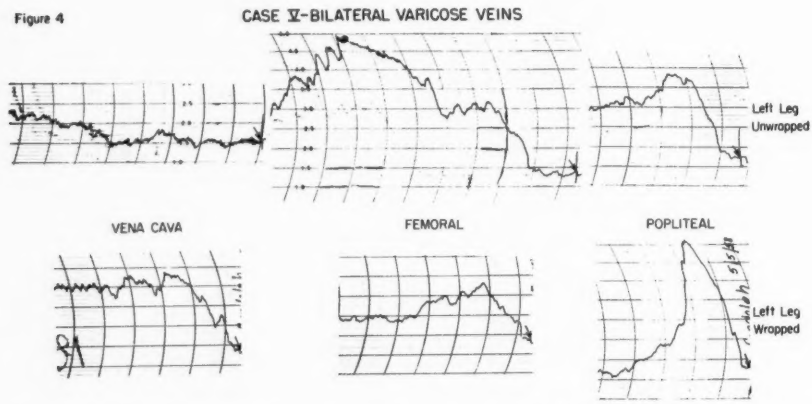

Figure 4. An isotope tracing in a patient with bilateral primary varicose veins. Elastic supports improved the venous flow.

Case 4. A 54 year old man with a history of old bilateral shrapnel injuries of the legs returned to the hospital with evidence of dilated, tortuous superficial leg veins. Isotope studies revealed a slow, gradual irregular rise of radioactivity with a prolonged circulation time. When the legs were wrapped there was only minimal improvement in the appearance of the tracings of the isotope studies. This suggested involvement of the deep venous system with the resultant formation of post-phelebitis incompetent superficial collaterals (Fig. 3).

Case 5. A 46 year old male with extensive varicose vein deformities of both lower extremities gave no history of previous thrombo-phlebitis. The isotope studies revealed a pattern of a slow irregular rise of radioactivity and longer circulation times not unlike those seen in the post-phlebitic limb. However, wrapping both limbs with supporting elastic bandages significantly shortened the circulation times and lessened the angles of radioactivity (Fig. 4).

Case 6. One week following inguinal herniorrhaphy, a 38 year old male had clinically diagnosed acute thrombo-phlebitis of the left leg and showed no abnormality of the right limb. Isotope studies compared with the normal right side indicated no significant alteration in circulation times or tracing angles. In this instance, damage to the deep venous system on the affected side had not progressed sufficiently to alter the course of the isotope. The clinical diagnosis was accepted, and the patient responded to conservative management uneventfully (Fig. 8).

Case 7. After a radical cleanout of incompetent superficial collateral vessels of the medial compartment of the right lower leg (similar to Linton's procedure (6), this patient had a marked delay in the passage of the isotope through the affected limb. The pattern was suggestive of marked chronic venous insufficiency (Fig. 9).

Case 8. A 46 year old colored female with a longstanding history of postpartum "milk leg" presented with marked swelling, induration, and ulceration of the left leg as well as pain and swelling in the right. The appearance was that of bilateral thrombo-phlebitis. No large veins were palpable in the edematous, indurated left limb. However, with a simple venapuncture using a No. 24 needle an isotope study revealed advanced chronic deep venous involvement (Fig. 10).

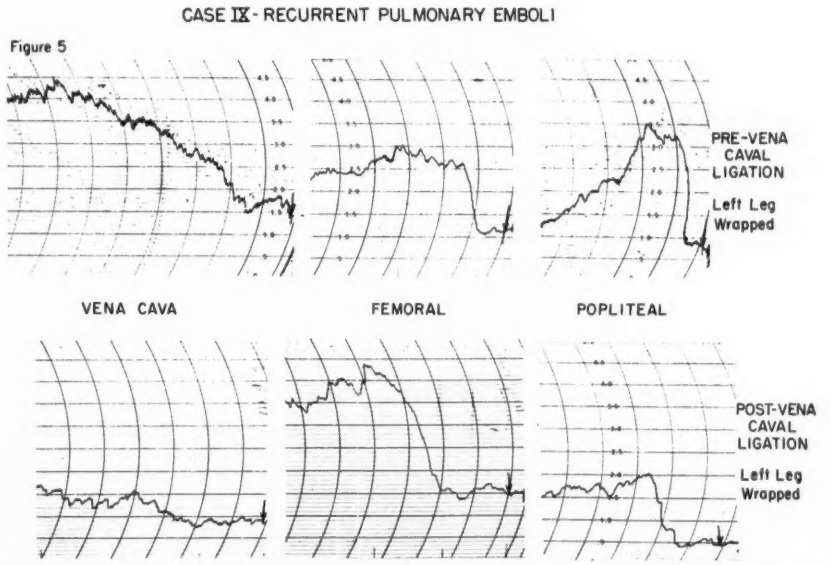

Figure 5. An isotope tracing in a patient with recurrent pulmonary emboli in whom the inferior vena cava was ligated.

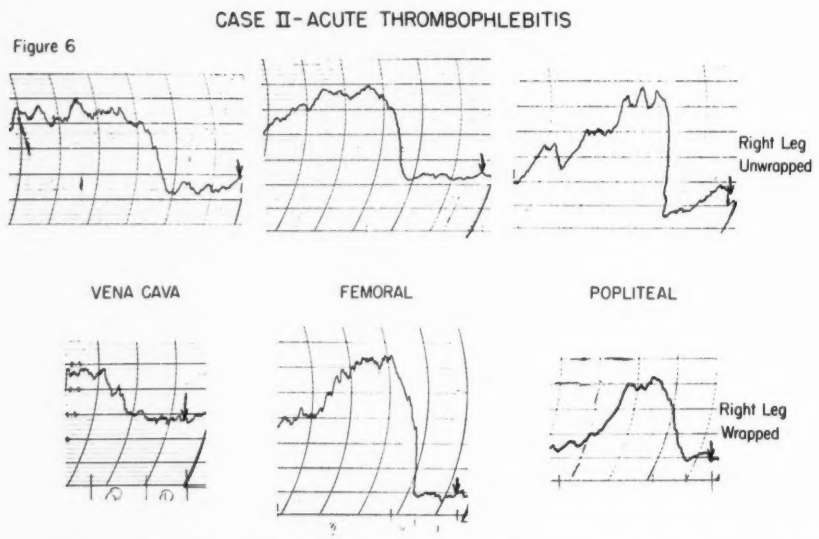

Figure 6. Acute thrombo-phlebitic disease in a previously normal limb did not alter the wave of radioactivity significantly.

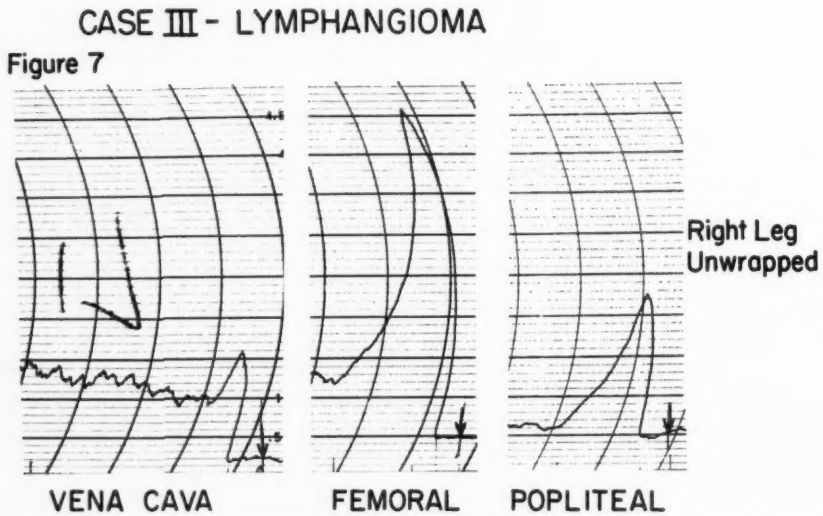

Figure 7. A normal study in a young boy with lymphagiomatous malformations of the right lower limb. No venous involvement was demonstrated by venography.

Case 9. A 74 year old physician underwent ligation of the inferior vena cava following a number of episodes of pulmonary embolism. There was no history or evidence of thrombophlebitis of the lower extremities, and deep pelvic (iliac) plebo-thrombosis was considered as the source of the emboli. Isotope studies following recovery indicated slight delay in the circulation times and a prolonged rise to the slope of radioactivity as compared to similar studies prior to ligation (Fig. 5).

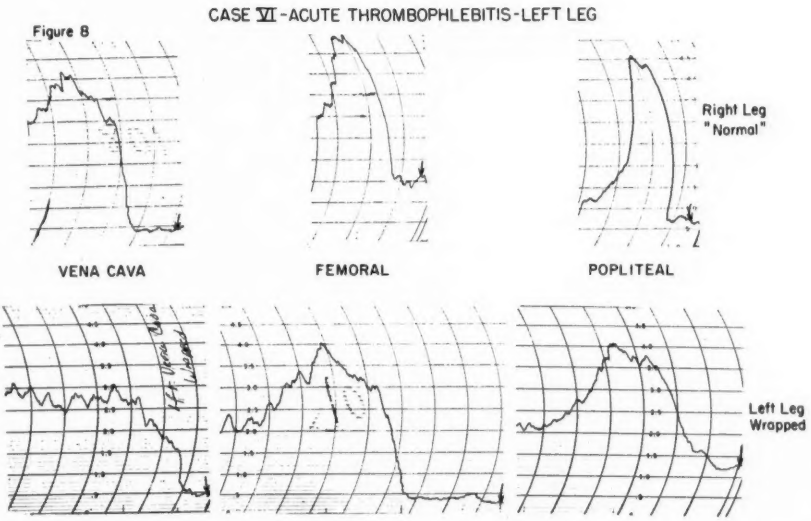

Figure 8. Slight alteration in the wave of radioactivity was seen in this patient with acute thrombo-phlebitis of the left leg following inguinal herniorrhaphy.

COMMENT

The principle of the venous isotope studies was based on the complexity of the venous route a predetermined amount of radioisotope must traverse in order to leave the affected limb, as well as the extent of the pathway involved. A delay in circulation time implied either a sluggish venous system (e.g., congestive heart failure) or an increase in the number of routes the blood must take (e.g., primary varicose veins, post-phlebitic incompetent superficial collaterals, etc.) thereby diluting and dispersing the radioactive material. A patent

deep system resulted in a sharp rise and clear-cut wave of radioactivity, while disease in the deep venous system resulted in a slow, gradual irregular rise in radioactivity as the dispersed stream passed near the counter.

Collapse of superficial varicose veins with elastic supports decreased the circulation times and caused a more rapid rise in the waves of radioactivity. As expected, the supported post-phlebitic limb did not show as much improvement as did the supported varicose veins.

Ligation of the inferior vena cava experimentally in previously normal dogs resulted in an increase in venous pressure in the lower limbs, a delay in the isotope circulation time and a diminished slope of the radioactivity curve. (2) However, in patients with advanced deep venous thrombo-phlebitic disease in whom vena cava ligations were done for repeated pulmonary embolization, the circulation times and waves of radioactivity approximated the normal. This was explained by the formation of numerous venous channels for collateral circulation which permitted rapid outflow from the venous system of the affected limb. In patients with pelvic venous thrombosis (which constituted 50 per cent of the overall patients with pulmonary emboli in the Duke University Hospital series (2) the appearance of the isotope at the first two counters was not necessarily affected to any great extent. The counter at the vena cava in these patients showed no evidence of patency at the point of ligation; circulation times and tracings were difficult to measure and interpret.

Venography and pressure studies using indwelling polyethylene catheters

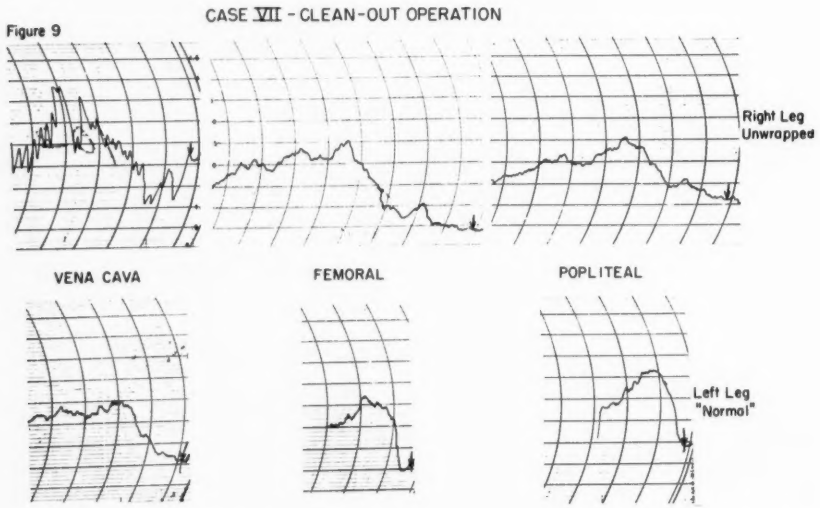

Figure 9. Following radical clean-out of incompetent superficial collateral vessels of the medial compartment of the right leg, the istope study was suggestive of marked chronic venous insufficiency.

are procedures not without hazard in the study of the already affected limb. Irritation with radiopaque solutions and prolonged intravenous fluid administration for pressure studies may enhance the further development of venous thrombosis. The use of only 0.5 ml of radioactive diodrast through a No. 24 needle into the dorsalis pedis vein is essentially a harmless procedure by which to evaluate the status of an affected limb and to discover the possible presence of unsuspected deep venous occlusive disease in a "normal" limb. I^{131}-tagged Diodrast, unlike I^{131}-tagged serum albumin, is excreted rapidly. No complications have occurred to date with the use of this isotope test.

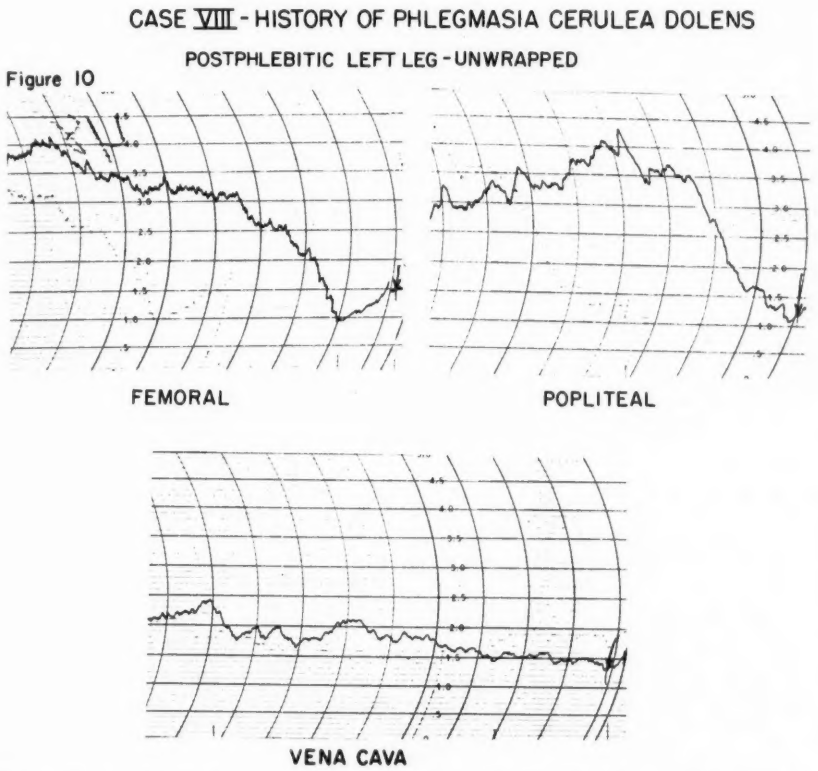

Figure 10. An abnormal venous isotope study in a patient with a long-standing history of post-partum phlegmasia cerulea dolens.

SUMMARY AND CONCLUSIONS

1. In addition to a careful history and physical examination, isoflow venography, venous pressure studies and isotope studies serve as useful adjuncts to obtain accessory information in the evaluation of patients with venous disease of the lower limbs.

2. The venous isotope test is a relatively safe, rapid, and simple procedure, and aids to determine the degree of deep venous involvement of the lower limbs. The test helps to differentiate between primary varicose veins and postphlebitic incompetent superficial collaterals.

3. The technique found most satisfactory and the results of normal and abnormal isotope outflow tests are described in 153 studies, including 44 postphlebitic, 10 inferior vena cava ligations, 14 primary varicose veins, one vascular malformation, and 84 normal controls.

4. The principles and applications of this test to a number of clinical situations involving the venous system of the lower extremity are discussed.

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The Topographic Distribution of Liver Metastases Its Relation to Surgical and Isotope Diagnosis[1]

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INTRODUCTION

A patient with distant organ metastasis cannot be cured by treatment of the primary lesion alone. For this reason pretherapy investigations are made for the purpose of locating any such foci. Large lesions in most organ and small foci (0.5 cm or larger) in bone, lungs and skin are readily recognized by current diagnostic methods. However, small lesions in the liver and other organs are difficult to discern.

Within the last five years, considerable efforts have been made for detection of the space occupying lesions in the liver by isotopic scanning methods, since no satisfactory contrast material has yet been found for radiographic visualization of these lesions.

Isotopic scanning appears to be a promising solution. It is a non-traumatic procedure and gives a negligible or minimal radiation dose to the body particularly when Rose Bengal I-^{131} is used (2).

Since the liver is a common site for metastasis, it is important to have a simple and accurate method to determine whether or not it is involved before initiating curative therapy. Furthermore, it is also important to discover the size of the metastatic lesions as well as their number.

MATERIALS AND METHODS

A series of 450 consecutive autopsies performed at Roswell Park Memorial Institute were studied.

Observations were made as to the presence of gross liver metastases and their locations, sizes and numbers and correlated to the size and weight of the liver. Whenever it was necessary, microscopic findings were also obtained.

RESULTS

Gross liver metastases were present in 150 cadavers (33 per cent of total). These findings were compatible with those reported by Satterlee (3) and Willis (4).

The sites of the primary lesions are shown in (Table 1). Other organs contain secondary cancer foci in 139 of the 150 cadavers but the liver was the only site of metastases in 11 cases. In 47 of the 150 cases lung metastases were also present.

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1. From the Department of Nuclear Medicine and Pathology, Roswell Park Memorial Institute, Buffalo, New York and the Department of Radiation Therapy, The Johns Hopkins University, Baltimore, Maryland.

In most instances both lobes of the liver were involved but when unilateral, the right lobe was more often involved than the left (Table 2).

The location of the liver metastases has been divided into those involving only the surfaces, only the internal parenchyma and both the surfaces and the internal parenchyma (Table 3).

In 16 cases (10.7 per cent) no deposits were visible or palpable on the surface of the liver, but cut sections, in these cases, revealed metastases. Superficial deposits, without evidence of intrahepatic lesions, were seen on the visceral surface in 6 and on the pariental surface in 22 cases.

TABLE 1

SITES OF PRIMARY LESIONS IN 150 CASES OF LIVER METASTASES:

Sites	*Number*
Breast	29
G. I. Tract	22
Lung	17
Renal Tract	13
Lymphoma and Leukemia	13
Ovary	11
Corpus Uteri	10
Esophagus	6
Cervix	5
Melanoma	5
Larynx	5
Gall Bladder	4
Urinary Bladder	3
Vulva	2
Miscellaneous	4
Unknown	1
TOTAL	150

TABLE 2

LOBE INVOLVEMENT BY METASTATIC CANCER

Right Lobe Only	*Left Lobe Only*	*Both Lobes*	*Total*
29	5	116	150

TABLE 3

LOCATION OF LIVER METASTASES

Surface Only	*Internal Parenchyma Only*	*Both Parenchyma and Surface*	*TOTAL*
28	16	106	150

The size of the liver was normal in 46 of the 150 cases (30 per cent). Therefore, it should be emphasized that the liver enlargement does not always accompany liver metastases.

The maximum diameter of the liver metastases was less than 2 cm in 47 of the 150 cases (31 per cent); this is very important because such lesions cannot be detected by the available isotopic scanning technique unless confluent nodules are present or they are located on the surface of the liver.

DISCUSSION

The current methods used to locate liver metastases preoperatively are (1) physical examination, (2) laboratory methods, (3) radiosotope scanning and (4) surgical exploration.

The inaccuracy of physical examination is obvious. One depends on the palpation of nodules. In 30 per cent of the cases with liver metastases the liver was normal in size and in both normal and enlarged livers some nodules could not be palpable because of their locations within the liver substance or on surfaces other than the anterior and inferior ones.

Liver function studies as a part of laboratory procedure, has considerable limitation for this purpose.

As to accuracy of surgical exploration, more than 10 per cent of the metastatic nodules were found to have no evidence of surface involvement; in addition, there were some instances in which liver metastases occurred only in the superolateral portion of the subdiaphragmatic surface and upper part of the posterior surface of the liver. It is exceedingly difficult to explore and palpate these portions of the organ. It is estimated from this study that more than 15 per cent of the cases with liver metastases would not have been detected by exploration. In these instances satisfactory liver scans may be helpful to detect some of these lesions.

Out of the 150 cases, there were only 11 cases in which the liver was the only site of metastases. Further observations revealed that among these 11 cases, 7 of them showed multiple metastatic nodules in both lobes. Thus there remained only 4 cases (2 per cent) in which single metastatic deposits were found, making them suitable for radical excision. This shows the extreme limitation of the surgical approach to the treatment of metastatic liver disease.

From these studies we have learned that a discrete, small space occupying lesion which is smaller than (2 cm) in diameter, could not be consistently detected. This is because of the limited resolution of the available scanning devices. (An ORNL 61 channel analyzer, a 3 inch focusing collimator used with a 3 inch diameter, 2 inch thick Na I (TL) crystal). (1).

Since 30 per cent of the cases with metastases have nodules smaller than 2 cm, this technique will fail to visualize metastases in a significant number of cases. However, some of the overlying or superficial lesions smaller than 2 cm in diameter may be detected occasionally.

When the patients are seen for initial therapy, one presumes that even fewer cases will have nodules as large or larger than 2 cm.

It is also important to realize that in vivo detection of lesions is not exactly comparable to the theoretical resolution attainable in vitro for the following reasons:

1. The organ constantly and appreciably moves during the scanning period; this motion shows many variations from an individual to individual, even variations in the same patient.
2. The scattering medium is not exactly the same in vivo as compared with a phantom.
3. Different thicknesses of the subcutaneous tissue, non-uniform uptake in the polygonal cells in different parts of the liver, the effects of ribs on the absorption and scatterning, all result in differences.

Other current laboratory procedures are not helpful in locating early and small metastatic foci. The problem of biopsy by needle puncture is self-evident because it is a blind study and small metastases would be frequently missed even if multiple biopsies were taken. Although scanning would be of help in directing the needle.

Even surgical exploration would fail to locate the metastases, as mentioned before in more than 15 per cent of the cases.

CONCLUSIONS

1. It has been shown by a careful study of cancer autopsies that liver metastases are of such size and locations that they frequently cannot be detected by current clinical methods which include physical examinations, laboratory procedures, isotope scanning and surgical exploration.

2. The extreme limitations of surgical approach to metastatic liver disease is discussed, in view of the finding that less than 2 per cent of the observed cases showed a single metastasis.

3. The most promising method is radioisotope scanning, but the technique needs refining in order to delineate small lesions, preferably ones in the magnitude of a fraction of a cm.

Such diagnostic methods would be of a great help as a guide to the proper therapy of the patient both when initially seen and in the post-treatment periods.

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Disposable Equipment For Use in Administering Therapeutic Quantities of Radioactive Isotopes[1]

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Sterile, disposable equipment which is now commercially available can be used for many procedures in a radioisotope laboratory. In addition to the advantage of convenience its use affords a simple solution to the problem of radioactive contamination of equipment. After it is used the equipment can be set aside for radioactive decay and later disposed of with no further handling.

An excellent flushing system for the administration of packaged therapeutic doses of radioactive isotopes, incorporating a by-pass feature, was devised by Karioris and Cowan (1). An adaptation of this system using disposable equipment is shown in Figure 1.

In use hemostats A and B are clamped initially and C is opened, permitting testing with normal saline. When it is assured that the saline is running well into the cavity or vein intended, hemostat C is clamped and B and A are opened. The saline is thereby directed through the isotope vial. When most of the saline has been used the hemostats are arranged in the initial conditions so that there is finally a flush of normal saline. This last maneuver reduces further the contamination of the needle or catheter which is to be removed. Keeping the long needle of the plasma aspirating set (Fig. 1, Item 5) below the level of the fluid in the isotope vial will prevent air from being introduced.

Upon completion of the injection the tubing assembly and isotope vial are not disconnected but rather are placed in a disposable container such as an unused milk carton and set aside for radioactive decay. When surveys indicate sufficient decay has occurred the assembly may be discarded without further handling.

When this assembly is used for intraperitoneal injections it is connected to a small plastic tube which was previously placed through the abdominal wall. The Becton-Dickinson Vinyl Tubing VX044, 0.065″ O. D. will just slide through a 14 ga thin-walled B. D. needle. The disposable 18 ga B. D. needle will fit snugly into this tubing.

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1. From the Department of Radiology, Latter-Day Saints Hospital, Salt Lake City, Utah.

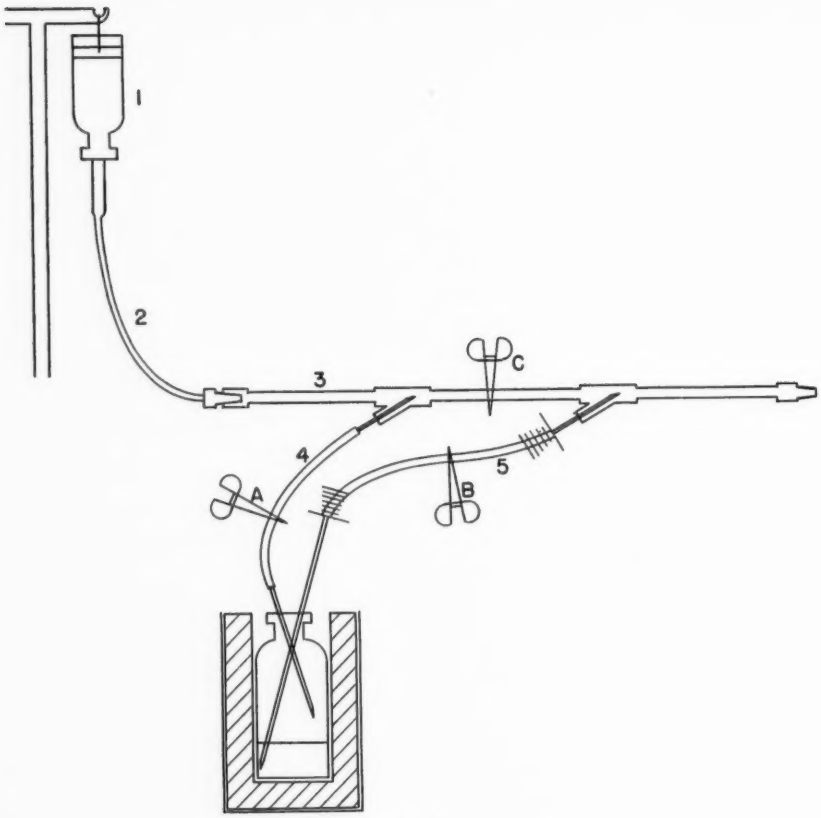

Fig. 1

Fig. 1. Tubing assembly. 1 and 2: Regular intravenous saline solution and tubing. 3: Abbott 4522 Twinsite Venotube. 4: B. D. 448 Duo-Purpose Blood Donor set (or same as item 5). 5: Baxter R-32 Plasma Aspirating Set (used because of long needle).

The efficiency of the flush method of delivery of radioactive isotopes has been generally recognized. This efficiency may be quantitated from an analysis of the simplified system shown in Figure 2.

Let:

V_f = Volume of the flushing saline.

V_i = Volume of the isotope solution in the vial (a constant)

A_o = Initial activity of the isotope solution in the vial.

A_f = Activity of the isotope solution in the vial after flushing with V_f amount of saline.

The activity of any infinitesimal volume of solution leaving the vial will be directly proportional to the activity and inversely proportional to the volume of the solution in the vial. This may be expressed by the equation:

$$-\frac{d\,A}{d\,V_f} = \frac{A}{V_1}$$

Integrating: $A_t = A_o\, e^{-V_f/V_1}$

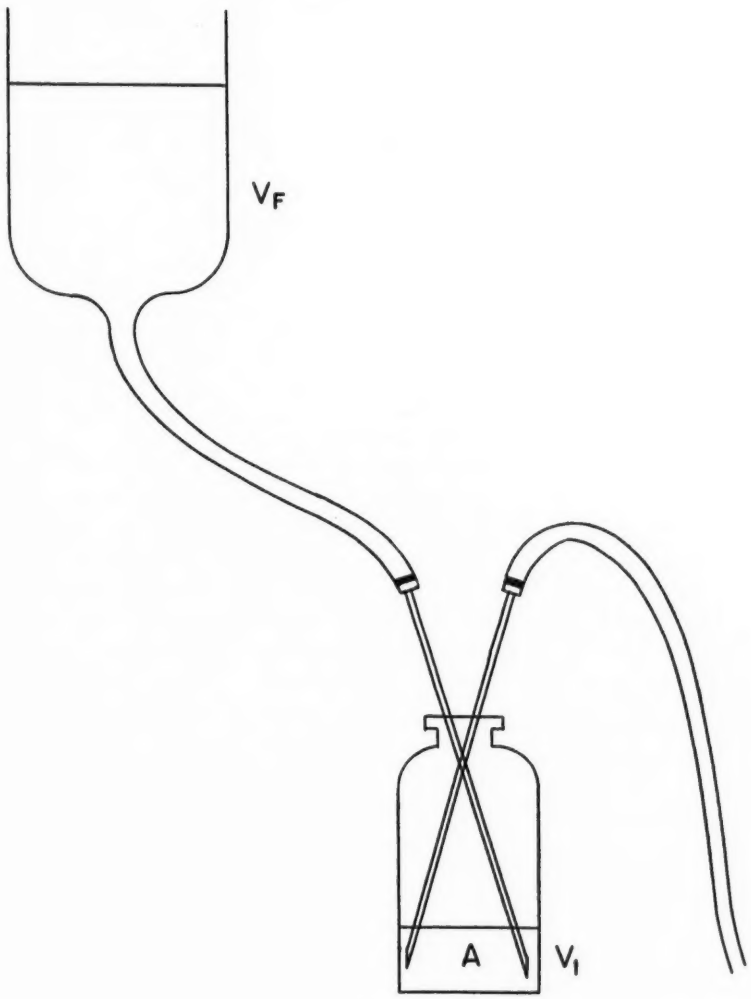

Fig. 2

Fig. 2. Standard Flushing Assembly.

The percent of dose flushed from the vial will be 100 $(1 - A_f)$. Representative values are given in Table 1.

TABLE 1. PERCENT OF RADIOISOTOPE DELIVERED FROM VIAL BY FLUSHING

V_f	$V_i = 5$ ml.	$V_i = 10$ ml.		$V_i = 15$ ml.		$V_i = 25$ ml.
	Calculated %	*Observed* %	*Calculated* %	*Observed* %	*Calculated* %	*Calculated* %
25 ml.	99	94	93	91	81	64
50 ml.	100	99	99	97	96	86
75 ml.	100	100	100	98	99	95
100 ml.	100	100	100	99	99	99

The above calculations are based upon the assumption that mixing of the flushing solution with the radioactive solution in the vial is instantaneous and complete. In actual practice, when the two needles are placed at some distance from each other, some of the isotope is delivered not by mixing but by displacement. Thus the experimental results given in Table 1 determined by measuring radioactivity in the vial using a shielded scintillation counter during flushing indicates a somewhat greater efficiency than do the calculated values. The small amount of flushing solution necessary for efficient delivery of the isotope is impressive.

SUMMARY

Commercially available, disposable equipment can be easily adapted to the administration of therapeutic doses of radioactive isotopes. The flush method of delivery is efficient as well as convenient.

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ADDENDUM

Since this paper was completed, the author has discontinued using a needle for introduction of the radioactive colloid into the pleural space, and instead uses a small vinyl catheter just as in the peritoneal cavity. After this catheter has been placed through the chest wall, a thoracentesis is performed using a separate puncture. This change has been made in order to minimze the hazards of injecting the radioactive material into the lung substance or into the tissues of the chest wall.

JOURNAL OF NUCLEAR MEDICINE 3:157, 1962

Salivary 'Protein Bound' Iodine[1]

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Boonton, N. J.

INTRODUCTION

Iodine secreted by the salivary glands may simulate a protein bound fraction. The generally accepted concept that iodine traversing the salivary glands does so in the inorganic state and therefore does not have to be considered when studying protein bound materials that may have saliva admixed–particularly gastric contents. Best and Taylor (1) noted that saliva is composed of 99.5 per cent water, 0.3 per cent organic solids and 0.2 per cent inorganic solids. The organic solids consist of a mixture of ptyalin, maltase, lysozyme, mucin, serum albumin, serum globulin, urea, uric acid, creatinine and amino acids. Beierwaltes (2) has stated that there is apparently an enzyme in the saliva which prevents the binding of radioactive iodine to the protein fractions. It is the authors contention that the iodine of saliva is bound to protein in varying amounts.

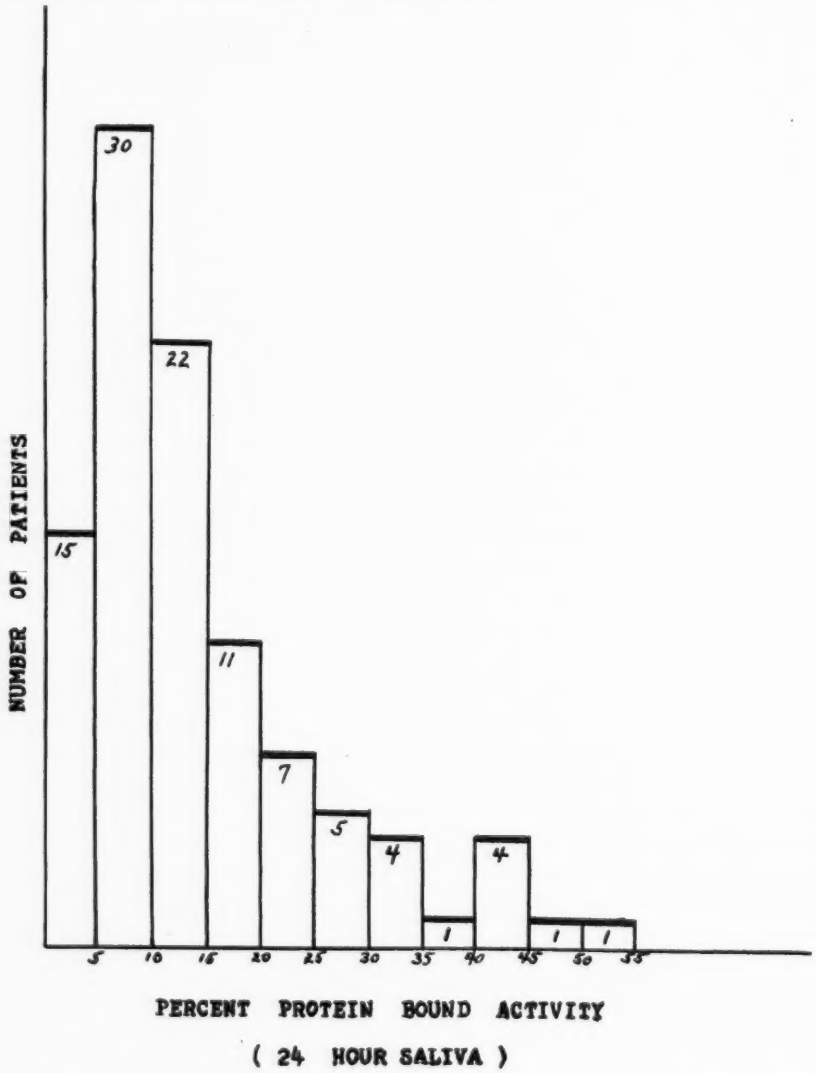
METHOD AND RESULTS

Saliva was collected from 100 patients who had received oral tracer doses of 50μc of I^{131} in the form of sodium iodide. The saliva was collected 24 hours after administration of the tracer dose, at which time thyroidal uptake and the conversion ratio were also determined. A 1.0 ml aliquot of the collected saliva was placed in a test tube and counted in the well scintillation counter. The net counts per minute varied from 243 to 116,162. Four milliliters of 10 per cent trichloracetic acid was then added to the test tube. The mixture was stirred with a wooden applicator, centrifuged, decanted, and washed three times with water. Two milliliters of 10 per cent sodium hydroxide and 1.0 ml of water were then added, mixed and counted in the well scintillation counter. The salivary 'protein bound' fraction was calculated as a percentage of the original saliva.

1. From the Radio-Isotopes Department, Bellevue Hospital, New York.

$$\frac{\text{Counts in precipitated saliva}}{\text{Counts in original saliva}} \times 100\% = \%\ \text{protein bound saliva}$$

It is noted (Fig. 1) that up to 54 per cent of the activity in the original saliva was still present in the precipitable bound fraction. The average was 14 per cent and the median was 10 per cent. Six check samples using the resin column method also showed similar results. Attempts to delineate the specific protein fractions by electrophoresis were not conclusive due to the technical difficulties encountered in moving the fractions. Further testing by other methods is indicated to solve this specific portion of the problem.



DISCUSSION

The experimental data show that varying amounts of radioactive iodine given orally as tracer doses becomes 'bound' to protein or behaves as protein and is secreted by the salivary glands. Stein et al (3) had stated that inorganic iodine is excreted by the salivary glands while Freinkel and Ingbar (4) found that salivary iodine was entirely inorganic. In the latter the salivary specimens were obtained within a few hours after administration of the tracer dose. Ferguson et al (5) in studying salivary secretions in hypothyroidism quoted Freinkel and Ingbar that there were negligible amounts of protein bound activity in saliva and therefore protein precipitation was not carried out before counting. Freinkel and Ingbar (6) also found that chromatographed specimens of saliva migrated as inorganic iodine, but again on samples taken after a few hours. Honour et al (7) found that in most cases the nonprecipitable fraction contained nearly all of the radioactive iodine, while in a few cases the precipitable radioactive iodine accounted for almost half of the total. They, however, did not pursue this any further. They concluded that the salivary glands concentrate iodine to an extent comparable with the trapping of iodine by the thyroid, suggesting that the salivary glands and thyroid possess a common iodide concentrating mechanism.

An attempt was made to correlate the precipitable salivary activity with the clinical status of the patient, the thyroidal uptake studies, and the conversion ratios. In most of the cases in which the protein bound salivary activity was high there was a low saliva count and an elevated thyroidal uptake and high conversion ratio of I^{131}. This suggested an additional test to estimate thyroid function, however, the many variable findings indicate the unreliability of the test for this purpose.

SUMMARY

Radioactive iodine secreted through the salivary glands is present as a 'protein bound fraction' in varying amounts. The procedure is unreliable as a test of thyroid function.

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JOURNAL OF NUCLEAR MEDICINE 3:160, 1962

Radiocyanocobalamine (Co^{57} B_{12}) Concentration in the Parathyroid Glands[1]

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PRELIMINARY PROGRESS NOTE[2]

Cobalt-60 labeled vitamin B_{12} has been reported to bind to pituitary and parathyroid tissue in concentrations higher than in other endocrine organs (1). It was suggested that vitamin B_{12} may play an important role in pituitary and parathyroid metabolism. We have investigated the possibility that cobalt-57 labeled vitamin B_{12} (Co^{57} B_{12}) may concentrate sufficiently in parathyroid tissue to permit localization of parathyroid glands by scintillation scanning techniques.

METHODS

Dog Experiments.

Three dogs were injected intravenously with 5 to 30 μc of Co^{57} B_{12}*, as shown in Table 1, after anesthesia was achieved with intravenous sodium pentobarbital. The specific activity of the injections varied from 0.93 to 5.0 μc/ug. Blood samples were withdrawn periodically. In the first two dogs right thyroid lobectomies with right parathyroidectomies were performed at approximately 4 hours after injection of Co^{57} B_{12}, and the contralateral thyroid lobe and parathyroids were removed at 24-29 hours after the injection. The third dog had both thyroid lobes and all parathyroid glands removed 4 hours after the injection. The dogs were sacrificed after the final operation in each case and other tissues were sampled. The tissues removed were carefully dissected free of visible extraneous structures and blotted. The radioactivity content was de-

[1]From the Department of Internal Medicine, the Clinical Radioisotope Unit and the Kresge Radioisotope Unit, University of Michigan Medical Center, Ann Arbor, Michigan.

This work was supported in part by the Isotope Unit Research Grant.

[2]Preliminary Progress Note: See Page 93.

*Obtained from Abbott Laboratories, Oak Ridge, Tennessee, as Racobalamin-57 for sterile injection. Part of the Co^{57} B_{12} was furnished as a gift by B. T. Eberle, M.D. of Abbott Laboratories in North Chicago, Illinois.

termined in a well-type scintillation counter with a pulse height selector. The parathyroid glands were confirmed histologically, and in no case was there more than a rim of thyroid tissue included.

In Vitro Photoscanning Studies.

To determine the sensitivity and resolving power of our photoscanner[1], mock experiments were performed. Blotting papers, varying from 0.5 × 0.5 cm. to 1 × 2 cm in size, were encased in waterproof tape after impregnation with Co^{57} B_{12} radioactivities totaling from 5 to 200 mμc. These radioactive mock parathyroid glands were initially photoscanned without added background radiation. Later the mock glands were immersed in 50 ml of water containing Co^{57} B_{12} in the concentration of 1 mμc and 5 mμc per milliliter. This background solution was 3 centimeters deep above and 1 centimeter deep below each mock gland when in position for scanning.

A rat was injected with 0.5 μc of Co^{57} B_{12} and was scarified 4 hours later. One rat kidney weighed 871 mgm and contained about 34 mμc. To demonstrate the detection of Co^{57} B_{12} within tissue, the kidney was photoscanned in an empty petrie dish.

RESULTS

Dog Experiments.

Plasma Disappearance Rate.

The plasma disappearance curve of Co^{57} B_{12} showed two different slopes. The first slope had a half-time (T½) of less than 10 minutes. The slower component had a T½ of 18 to 23 hours. Less than 4 per cent of the injected radioactivity remained in the intravascular space after 4 hours[2].

Concentration of Co^{57} B_{12} in Organs.

The concentration of Co^{57} was about 10 fold greater in parathyroid tissue than in muscle and plasma, and 4 to 7 times greater than in skin as shown in Table 1. The concentration of Co^{57} in thyroid tissue was the same as, or slightly higher than, in the parathyroid glands. The high affinity of kidney, liver, spleen and lymph nodal tissue for B_{12} previously has been noted (3).

In Vitro Photoscanning Studies.

The minimum radioactivity of Co^{57} detected by the photoscanner was about 10 mμc without added background activity as shown in the Figure 1a. The lowest mock activity detected with certainty in a background of 1 mμc/ml was 20 mμc as shown in the Figure 1b. In a higher background of 5 mμc/ml, 50 mμc and 100 mμc in the mock parathyroid gland were recorded by the photoscanner, but 20 mμc is poorly defined (Figure 1c and 1d).

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[1]Picker Magnascanner with a 19-hole collimator obtained from the Picker X-ray Corporation, 1275 Mamaroneck Avenue, White Plains, New York.

[2]Plasma space was determined by the formula:

$$\text{Plasma volume} = 205 + (34.4 \times \text{Kg of wt.}) \qquad (2)$$

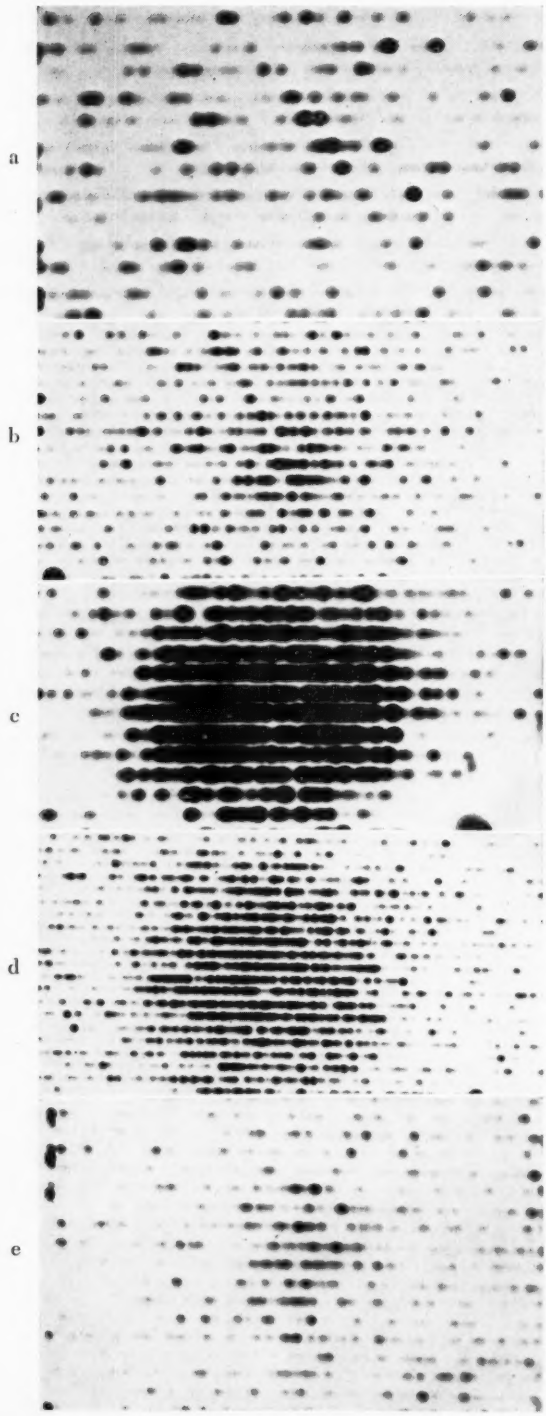
TABLE 1—Data on radioactivity of tissue specimens of three dogs injected intravenously with 5 to 30 μc of Co^{57} B_{12}. Counts were obtained in a scintillation well-type counter using a spectrometer.

Tissue Specimens	*Weight (Mg)*	*Net CPM*	*CPM Per Mg Tissue*	*% of Injected Dose*
Dog #1 (Co^{57} B_{12} 5 μc, specific activity 0.936 μc/ug)				
At 4 hrs.				
Right Parathyroid A	17.9	34.6	1.93	0.00034
Right Parathyroid B	23.8	57.8	2.43	0.00057
Right Thyroid	184.8	524.1	2.84	
Right Strap Muscle	134.4	36.1	0.27	
Plasma 1 ml	1,000.0	248.7	0.25	
At 24 hrs.				
Left Parathyroid A	26.8	40.2	1.50	0.00040
Left Parathyroid B	14.2	11.7	0.82	0.00012
Left Thyroid A	187.3	347.2	1.85	
Left Thyroid B	144.7	254.7	1.76	
Left Strap Muscle	314.2	82.2	0.26	
Plasma 1 ml	1,000.0	120.7	0.12	
Liver	1,278.3	371.7	0.29	
Dog #2 (Co^{57} B_{12} 30 μc, specific activity 1.17 μc/ug)				
At 4½ hrs.				
Right Parathyroid	22.4	276.2	12.3	0.00051
Right Thyroid A	72.4	1,166.9	16.1	
Right Thyroid B	55.0	945.6	17.2	
Right Strap Muscle	192.7	1,667.0	1.1	
Plasma 1 ml	1,000.0	204.6	1.7	

TABLE 1—*Continued.*

TABLE 1—*Continued.*

Tissue Specimens	*Weight (Mg)*	*Net CPM*	*CPM Per Mg Tissue*	*% of Injected Dose*
At 29 hrs.				
Left Parathyroid	7.4	82.0	11.1	0.00015
Left Thyroid A	62.8	951.0	15.1	
Left Thyroid B	59.4	819.0	13.8	
Left Strap Muscle	338.8	498.0	1.5	
Plasma 1 ml	1,000.0	729.0	0.7	
Liver	547.2	13,840.0	25.3	
Spleen	220.4	3,999.0	18.1	
Kidney	1,009.7	32,614.0	32.3	
Adrenal	105.0	61.0	0.6	
Ovary	474.0	3,106.0	6.6	
Skin	524.8	966.0	1.8	
Dog #3 (Co^{57} B_{12} 27.5 μc, specific activity 5 μc/ug)				
At 4 hrs.				
Right Parathyroid	11.8	304.0	25.8	0.00055
Left Parathyroid	8.6	234.0	27.2	0.00042
Right Thyroid	287.1	8,177.0	28.5	0.0148
Left Thyroid	243.9	9,412.0	27.4	0.0170
Left Strap Muscle	341.7	930.0	2.7	
Plasma 1 ml	1,000.0	3,404.0	3.4	
Liver	150.5	4,644.0	30.9	
Spleen	41.7	1,679.0	40.3	
Kidney	285.4	31,622.0	110.8	
Skin	98.7	715.0	7.2	
Tongue	88.2	575.0	6.5	
Lymph Nodes	426.2	10,680.0	25.1	0.0193


a
b
c
d
e

The size of the mock parathyroid was not critical for detection over the range of 0.5 × 0.5 cm to 1 × 2 cm used in the experiments. Although 20 mμc appeared more distinct in a 1 × 1 cm area than when diffused over an area of 1 × 2 cm, 10 mμc was not recorded differently in the 0.5 × 0.5 cm and the 1 × 2 cm mocks.

In Figure 1e, the photoscan of the rat kidney demonstrates, when concentrations of Co^{57} B_{12} similar to those utilized in the experiments with the mock parathyroid glands are incorporated into 871 mgm of tissue, no limitation to detection is imposed by self-absorption and backscatter of radiation, and other physical factors.

DISCUSSION

In the mock experiment a radioactivity of 1 mμc per milliliter of background did not interfere with the photoscanning detection of a 20 mμc source. This background activity corresponds to the concentration in plasma and muscle (1 mμc per gram of tissue) when a dog is administered 27.5 μc of Co^{57} B_{12}. A parathyroid gland in this same dog concentrated a total of 0.00055 per cent of the administered dose, or 0.15 mμc. Thus, to be able to photoscan *in vivo*, a parathyroid gland within a similar muscle and plasma background, at least 20 mμc should be concentrated within the gland, or about a 100 to 200 fold increase over the total concentration achieved in the dogs here.

Theoretically, this increase in total content of radioactivity would occur if the parathyroid increased in weight from .015 gm to 1.5 gm with the tissue concentration remaining constant. Such an increase in weight occurs occasionally in the clinical state of hyperparathyroidism in humans. In the 5 years from 1955 to 1960, the University of Michigan Medical Center Pathology Department received 14 surgically removed parathyroid adenomas. Although measurements were not available on all specimens, at least 5 were of a size to weigh more than 1 gram.

The 100-fold increased Co^{57} content of a parathyroid gland might be achieved in a parathyroid adenoma or in hyperplasia of the parathyroid gland without a 100-fold increase in weight of the gland, if the increased secretory activity of the gland were accompanied by a proportionate increase in concentration of Co^{57} B_{12} by the hyperactive gland.

Although these considerations make it theoretically possible to locate enlarged hyperfunctioning parathyroid glands in man, the concentration of Co^{57} B_{12} in the liver and other tissues with high levels of radioactivity constitute a

Fig. 1. Photoscans of mock parathyroid gland specimens. Mocks a through d were made of blotting papers of various sizes encased in waterproof tape after impregnation with Co^{57} B_{12}. Co^{57} B_{12} background radioactivity was varied. a. 10 mμc of Co^{57} B_{21} in 0.5 × 0.5 cm blotting paper without radioactive background. b. 20 mμc in 0.5 × 1 cm of paper in a background of 1 mμc/ml. c. Right half is 50 mμc in 1 × 1 cm and left half 100 mμc in 1 × 2 cm paper in background of 5 mμc/ml. d. 20 mμc in 1 × 1 cm paper in background of 5 mμc/ml. e. In vitro photoscan of rat kidney weighing 871 mgm labeled in vivo with 34 mμc of Co^{57} B_{12} without radioactive background.

(Legend for illustration on page 164)

formidable problem. If the liver concentration of Co^{57} were reduced, a higher percent of the administered tracer dose might be available for binding within the parathyroid glands.

The radiation received from administered cobalt-57 is 29-fold less than that from cobalt-60 (4). The reduction of radiation results from the shorter physical half-life of Co^{57} (270 days versus 5.2 years for Co^{60}) and the absence of beta ray emission in the Co^{57} decay. Nevertheless, attempts must be made to increase the ratio of Co^{57} B_{12} concentration in the parathyroid gland to the concentration in the liver.

Perhaps a loading dose of stable B_{12} injected at an appropriate interval before the radioactive dose may decrease the total amount of Co^{57} B_{12} accumulated in the liver while not affecting parathyroid concentration. This would permit a larger radioactivity injection with safety. A low calcium diet may stimulate parathyroid gland function with a concurrent increase in Co^{57} B_{12} uptake by these glands.

We are investigating the possibility that the thyroid gland accumulation of Co^{57} B_{12} may be suppressed by the administration of triiodothyronine. This suppression is essential to develop the low neck background radioactivity necessary for differentiating the parathyroid activity.

Because of the high cost and relatively long physical half-life of Co^{57}, the possibility of replacing the cobalt with a short half-life isotope of rhodium or iridium within the B_{12} molecule should be considered. If such elements prove to have a similar biological fate when combined with B_{12}, photoscanning will be equally good with a substantial reduction in radiation and possibly cost.

SUMMARY

Co^{57} B_{12} concentration in the parathyroid gland was found to be 10 times greater than concentrations in muscle and plasma of the dog. Concentrations in the thyroid gland were similar to those in parathyroid tissue. Scintillation photoscanning of the parathyroid gland utilizing labeled B_{12} is theoretically possible if the total amount of Co^{57} taken up by the gland exceeds 20 millimicrocuries. A parathyroid adenoma weighing greater than 1 gram will probably concentrate sufficient Co^{57} B_{12} for photoscanning under the conditions employed in this investigation. Thyroid tissue concentration of Co^{57} B_{12} will require suppression when photoscanning is performed to seek the parathyroid glands in the region of the thyroid gland.

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THE SOCIETY OF NUCLEAR MEDICINE

Ninth Annual Meeting

Baker Hotel

Dallas, Texas

Scientific Program

WEDNESDAY, JUNE 27, 1962

Morning Session

Registration—Mezzanine

9:00—Nominating Committee—TALLY HO ROOM

10:00—Joint Meeting of Board of Trustees and Executive Committee—ENGLISH ROOM

12:00—Executive Committee and Board of Trustees Luncheon—TALLY HO ROOM

1:30—Joint Meeting of Board of Trustees and Executive Committee—ENGLISH ROOM

Afternoon Session

International Session —S— CRYSTAL BALLROOM

Chairman: JOSEPH STERNBERG, M.D., Montreal, Canada.

From 3:00 P.M. until 5:00 P.M., several internationally known scientists will present papers dealing with recent advances in nuclear medicine in their respective countries. All members and guests of the Society are invited to attend this informative session.

Evening Session

SESSION A

CRYSTAL BALLROOM

Chairman: LINDON SEED, M.D., Chicago, President, Society of Nuclear Medicine

8:00 Welcome to Dallas—J. R. MAXFIELD, JR., Dallas, Texas

8:15 What We Accomplished—L. SEED, Chicago, Illinois

8:30 What We Hope to Accomplish—J. R. MAXFIELD, JR., Dallas, Texas

8:45 What We Have to Work With—W. H. BEIERWALTES, Ann Arbor, Michigan

9:00 Problems of a Professional Nature—L. FARR, Upton, L.I., New York

9:15 Our Relations With Our Helpers—E. KAPLAN, Hines, Illinois

9:30 Our Publication—G. THOMA, St. Louis, Missouri

9:45 Medical Nuclear Development in the U. S. Air Force Hospitals—D. LIVERMORE, Washington, D. C.

10:00 New Licensing Policies of A.E.C.

THURSDAY, JUNE 28, 1962

Morning Session—CRYSTAL BALLROOM

8:30 A.M. Registration—MEZZANINE

SESSION B

Clinical Diagnosis

Chairman: MILLARD N. CROLL, M.D., St. Davids, Pennsylvania

9:00 A.M. Tagged Isomers and Analogues of Thyroxin Transmission Across the Human Placenta.
J. E. KEARNS and HERBERT PHILIPSBORN, Evanston. B 1.*

9:15 A.M. 1200 T-3 Procedures.
BRUCE SODEE, Washington, D. C. B 2.

9:30 A.M. Comparative Thyroid Function Studies with the Resin T-3 Test.
FRANCIS FOECKLER, NELLIE MAY BERING, JOANNE SIRAGUSA, and OSCAR B. HUNTER, JR., Washington, D. C. B 3.

9:45 A.M. Statistical Analysis of the "Hamolsky-RBC-T-3" Test As Compared with the "Sephadex-T-3" Test.
J. L. RABINOWITZ and BERNARD SHAPIRO, Philadelphia. B 4.

10:00 A.M. Exhibit Break

Chairman: ERVIN KAPLAN, M.D., V. A. Hospital, Hines, Illinois

10:30 A.M. Liver Uptake of Rose Bengal I^{131} in Gastrointestinal Bleeding.
ISMAEL MENA, VICENTE VALDIVIESO, CATALINA MAGGIOLD, and ENRIQUE MONTERO, Santiago, Chile. B 5.

10:45 A.M. The Use of 24 Hour Blood Levels of I^{131}-labeled Rose Bengal Dye in the Differential Diagnosis of Jaundice.
NORMAN B. ACKERMAN and ARTHUR S. MCFEE, Minneapolis. B 6.

11:00 A.M. A Comparison of Thyroid Function Tests: the 6- and 24-hour Thyroidal Uptake, T-3 Red Cell Uptake, T-3 Resin Uptake, Reflex Recording and the PBI.
R. A. NORDYKE, A. M. BRAULT, and A. TONCHEN, Honolulu. B 7.

11:15 A.M. Radioiodine-123.
WILLIAM G. MYERS and HAL O. ANGER, Columbus and Berkeley. B 8.

11:30 A.M. The Use of I-125 in Clinical Nuclear Medicine.
LESTER M. LEVY, TERESITA, T. ESTRELLADO, OKOGBUE OKEZIE and H. S. STERN, Long Island. B 9.

Letter and number following each title in the Program refer to the corresponding abstract. The abstracts have been arranged by session and by order of presentation, and appear in the special convention issue of The Journal of Nuclear Medicine *(May, 1962, issue).*

11:45 A.M. The Cobalt-60 Vitamin B-12 Test—The Interpretation of Borderline Values.
BEN I. FRIEDMAN, EUGENE L. SAENGER, and ROBERT RUSKIN, Cincinnati. B 10.

12:00 Noon Buffet Lunch* and Exhibit Viewing

THURSDAY, JUNE 28, 1962

Morning Session—FIESTA ROOM

8:30 A.M. Registration—MEZZANINE

SESSION C

Biochemistry and Physiology

Chairman: JOSEPH P. KRISS, M.D., Standford Medical Center, Palo Alto

9:00 A.M. Ca^{47} Studies in Man.
E. MILLER, C. J. HLAD, JR., M. ERVIN, and H. ELRICK, Denver. C 1.

9:15 A.M. Some of the Factors Affecting Interpretation of Studies Employing a Single Intravenous Injection of Ca^{45}.
RICHARD GOLDSMITH, MILDRED J. WIESTER, and WENDELL M. RIDDELL, Cincinnati. C 2.

9:30 A.M. Na-22 Secretion in Sweat.
H. W. WEIGEL, J. PARSONS, C. J. HLAD, JR., E. MILLER, and H. ELRICK, Denver C 3.

9:45 A.M. The Relative Flow Rates of Red Cells and Plasma in Hypotensive Dogs.
MILTON G. CRANE, JOHN E. HOLLOWAY, RALPH ADAMS, and IVOR C. WOODWARD, Los Angeles. C 4.

10:00 A.M. Use of a Whole Body Counter in Turnover Studies of Ca-47 and Fe-59.
THORNTON SARGENT, MYRON C. POLLYCOVE, JOHN A. LINFOOT, and JOHN H. LAWRENCE, Berkeley. C 5.

10:15 A.M. The Clearance of Labeled Particulate Matter from the Human Tracheo-Bronchial Tree as Determined by External Monitoring.
ANGELO TOIGO, JOHN J. IMARISIO, HUNTER MERMALL and M. LEPPER, Hines, Illinois. C 6.

10:30 A.M. Exhibit Break

Chairman: CHARLES J. HLAD, JR., M.S., Denver, Colorado.

**On Thursday and Friday (June 28 and 29) a buffet luncheon, moderately priced will be served in the Terrace Room (17th floor). On Thursday the speakers from Session B (Crystal Ballroom) and Session C (Fiesta Room) will be available in the Terrace Room for discussion and to answer questions regarding their individual presentations.*

On Friday, at noon, the speakers from Session D, E, F, and G, will be available in the Terrace Room.

There will be no Buffet Luncheon on Saturday. The cost for these buffet luncheons will be $3.00. Tickets, subject to capacity limitations, will be available at the registration desk.

11:00 A.M. Factors Influencing the Incorporation of Radioactive Halogenated Pyrimidines into the DNA of Normal and Neoplastic Tissue *in vivo.*

JOSEPH P. KRISS and LASZLO REVESZ, Palo Alto. C 7.

11:15 A.M. Passage of Fe-labeled Erythrocytes into the Systemic Circulation.

F. KEITH BRADFORD and PHILIP C. JOHNSON, JR., Houston. C 8.

11:30 A.M. The Identification of True Chylous Effusions with Radioiodinated Trioleate.

PHILLIP RUBIN, ALVIN URELES, CHARLES SHERMAN, and JEROLD GREEN, Rochester, New York. C 9.

11:45 A.M. Determination of Blood Volume Distribution by Whole Body Counting.

GUNNAR SEVELIUS, DANIEL R. PATRICK, BETTY O'CONNOR, ELAINE PATRICK, and BILL COLEMAN. Oklahoma City. C 10.

12:00 Noon Buffet Lunch* and Exhibit Viewing

THURSDAY, JUNE 28, 1962

Afternoon Session—FIESTA ROOM

SESSION D

Circulatory and Pulmonary Phenomena

Chairman: L. R. BENNETT, M.D., UCLA Medical Center, Los Angeles.

2:00 P.M. The Possibilities and Limitations of Flow Measurements by External Counting.

BENEDICT CASSEN, Los Angeles. D 1.

2:20 P.M. Clinical Experience with the Coronary Flow Index.

HARRY BISHOP and ISMAEL MENA, Los Angeles and Santiago, Chile. D 2.

2:40 P.M. Coronary Blood Flow by Radiographic Technique, ECG and Clinical Diagnosis—A Correlation Study.

GUNNAR SEVELIUS, DANIEL R. PATRICK, BETTY O'CONNOR, ELAINE PATRICK, and BILL COLEMEN, Oklahoma City. D 3.

3:00 P.M. The Coronary Index.

ISMAEL MENA and HARRY BISHOP, Santiago, Chile, and Los Angeles. D 4.

3:20 P.M. Cerebral Circulation Studies.

W. H. OLDENDORF, Los Angeles. D 5.

3:40 P.M. Exhibit Break

Chairman: DONALEE TABERN, Ph.D., Lake Bluff, Illinois.

4:10 P.M. Pulmonary Function Studies Using Krypton-85.

HYO H. BYUN, GESILA ALBRECHT, GEORGE W. HOLMES and ROBERT S. LANAUER, Chicago. D 6.

**See 12:00 noon—Session B (page 169)*

4:25 P.M. Radio-pulmonography: A Simple Method for Simultaneous Estimation of Individual Lung Function.
M. J. SMALL, W. N. MILLER, G. C. LEINER, H. D. STRAUSS, and S. ABRAMOWITZ, East Orange. D 7.

4:40 P.M. Diagnosis of Shunts with Intracardiac Proportional-Counter Catheters—Preliminary Report.
MARSHALL B. KREIDBERG, CHARLES V. ROBINSON, and HARVEY L. CHERNOFF, Boston. D 8.

EVENING SOCIAL HOUR AND ANNUAL BANQUET

FIESTA ROOM and TERRACE ROOM (17th Floor)

6:45— 7:45 Social Hour-Cocktails (cash bar) FIESTA ROOM
8:00— 9:00 Annual Banquet (Dress Optional) TERRACE ROOM
9:00— 9:30 THIRD ANNUAL ADDRESS—NUCLEAR PIONEER SERIES
Presiding: LINDON SEED, M.D., Chicago
President, Society of Nuclear Medicine.
Introduction and Presentation of Scroll: Donalee L. Tabern, Ph.D., Chicago, Chairman, 1962 Program Committee.
Guest of Honor and Recipient of THIRD ANNUAL-NUCLEAR PIONEER LECTURE SCROLL: Glen T. Seaborg, Ph.D., Chairman, Atomic Energy Commission, Washington, D. C.
9:30—12:00 Dancing TERRACE ROOM
9:30—12:00 Smoker and "Shop Talk" FIESTA ROOM

THURSDAY, JUNE 28, 1962

Afternoon Session—CRYSTAL BALLROOM

SESSION E

Radiation Effects and Therapy

Chairman: JAMES R. MAXFIELD, JR., M.D., Dallas, Texas

2:00 P.M. The Association of Thyroid Cancer and Prior Radiation in Infancy and Childhood.
RAYMOND G. ROSE, J. H. HARTFIELD, and ELEANOR MACDONALD, Houston. E 1.

2:15 P.M. Radioactive Yttrium (Y-90) in Interstitial Therapy.
JOSEPH GREENBERG and H. C. DUDLEY, New York. E 2.

2:30 P.M. The Use of Intravenous P^{32}-labeled Colloidal Chromic Phosphate for the Prevention of Liver Metastases in Rats.
NORMAN B. ACKERMAN, ARTHUR S. MCFEE, and MERLE K. LOKEN, Minneapolis. E. 3.

2:45 P.M. Irradiation with Interstitial Radioactive Palladium.
I. ARIEL and J. S. ROBERTSON, New York City and Upton, Long Island. E 4.

3:00 P.M. Changes in Hepatic Function Following Hepatic Irradiation by Y^{90} Microspheres.
THOMAS GUZMAN, MERLE K. LOKEN, HARLAN ROOT, and JOHN S. PERRY, JR., Minneapolis. E 5.

3:15 P.M. Exhibit Break

Chairman: HENRY L. JAFFE, M.D., Cedars of Lebanon Hospital, Los Angeles.

3:45 P.M. Organ Irradiation by Means of Radiating Microspheres.
IRVING M. ARIEL, New York. E 6.

4:00 P.M. The Simultaneous Intraperitoneal Administration of Nitrogen Mustard and Colloidal Radioactive P^{32} in the Rat: Gross and Histopathological Findings.
LEONARD M. LIEGNER and NORMAN J. MICHAUD, New York. E 7.

4:15 P.M. Intravenous Colloidal Zirconyl Phosphate-P-32, Clinical Studies in Over 250 Cases.
J. M. HILL, E. LOEB and R. J. SPEER, Dallas. E 8.

4:30 P.M. Selective Tumor Response to Neutron Capture Therapy of Transplantable Neoplasms in the Mouse.
LEE E. FARR and T. KONIKOWSKI, Upton, Long Island. E 9.

4:45 P.M. The Comparative Lethal Radiation Dose of P-32 when Administered as Mono-Phosphate and Polymetophosphate.
ROGER VEATCH and ERVIN KAPLAN, Hines, Illinois. E 10.

5:00 P.M. Hematologic and Tumor Response to Low Dose Uniform Total Body Irradiation.
MELVILLE L. JACOBS, Duarte, California. E 11.

EVENING SOCIAL HOUR AND ANNUAL BANQUET

FIESTA ROOM and TERRACE ROOM (17th Floor)

6:45— 7:45 Social Hour-Cocktails (cash bar) FIESTA ROOM

8:00— 9:00 Annual Banquet (Dress Optional) TERRACE ROOM

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Introduction and Presentation of Scroll: Donalee L. Tabern, Ph.D., Chicago, Chairman, 1962 Program Committee.
Guest of Honor and Recipient of THIRD ANNUAL-NUCLEAR PIONEER LECTURE SCROLL: Glen T. Seaborg, Ph.D., Chairman, Atomic Energy Commission, Washington, D. C.

9:30—12:00 Dancing TERRACE ROOM

9:30—12:00 Smoker and "Shop Talk" FIESTA ROOM

FRIDAY, JUNE 29, 1962

Morning Session—CRYSTAL BALLROOM

8:30 A.M. Registration—MEZZANINE

SESSION F

Scanning

Chairman: HENRY N. WAGNER, JR., The Johns Hopkins University, Baltimore.

8:30 A.M. Statistical Analysis of Eight Years Experience in Positron Scanning for Brain Tumor Localization.
SAUL ARONOW, GORDON L. BROWNELL, SARA L. LOVO, and WILLIAM H. SWEET, Boston. F 1.

8:45 A.M. Body-Section Radioisotope Scanning.
DAVID E. KUHL and ROY Q. EDWARDS, Philadelphia. F 2.

9:00 A.M. Demonstration of Myocardial Infarcts by Photoscanning.
EDWARD A. CARR, JR., WILLIAM H. BEIERWALTES, AUDREY V. WEGST and JOHN D. BARTLETT, JR., Ann Arbor. F 3.

9:15 A.M. The Interpretation of Renal Photoscans.
RAYMOND S. KIBLER, MONTE BLAU, and MERRILL A. BENDER, Buffalo. F 4.

9:30 A.M. Renal Scanning.
PRENTISS M. DETTMAN and R. T. BROOKS, Bethesda. F 5.

10:00 A.M. Stop-flow Renal Scans.
J. L. IZENSTARK, J. U. SCHLEGEL, and R. O'DELL, New Orleans. F 6.

10:15 A.M. Diagnosis of Splenic Disease by Radioisotope Scanning.
HENRY N. WAGNER, JR. and JOHN G. MCAFEE, Baltimore. F 7.

10:30 A.M. Exhibit Break

Chairman: MERRILL A. BENDER, M.D., Buffalo.

11:00 A.M. Localization of Antifibrin Antibodies in Human Tumors.
W. C. DEWEY, W. F. BALE, R. G. ROSE, and D. MARRACK, Houston and Rochester, New York. F 8.

11:15 A.M. The Clinical Use of the Autofluoroscope.
MERRILL A. BENDER and MONTE BLAU, Buffalo. F 9.

11:30 A.M. Clinical Experience with Se^{75}-Selenomethionine for Pancreas Visualization.
MONTE BLAU, ROBERT F. MANSKE and MERRILL A. BENDER, Buffalo. F 10.

11:45 A.M. Liver Function as Related to Thyroxine Metabolism.
L. VAN MIDDLESWORTH, JO AUDREY TURNER, and ALYS LISCOMB, Memphis. F 11.

12:00 Noon Buffet Lunch* and Exhibit Viewing

**See 12:00 noon—Session B (page 169)*

FRIDAY, JUNE 29, 1962

Morning Session—FIESTA ROOM

8:30 A.M. Registration—MEZZANINE

SESSION G

Drug Metabolism

Chairman: MYRON POLLYCOVE, M.D., University of California, Berkeley, Calif.

8:30 A.M. Distribution, Excretion and Metabolism of C-14 Etryptamine Acetate in Man.
JOHN H. NODINE, JOSEPH M. PLATT, and ARNOLD DUCANES, Philadelphia. G 1.

8:45 A.M. Fate of Alykylated 6-S^{35}-Mercaptopurine in the Rat.
HANS J. HANSEN, GARY GILES, and SAMUEL B. NADLER, New Orleans. G 2.

9:00 A.M. Radioactive Modified Insulin: Method of Preparation and Comparison with Radioactive Crystalline Insulin in Human Subjects.
LEONARD R. ROBBINS, DAVID DWIGHT ODOM, PHILIP C. JOHNSON and HAROLD L. DOBSON, Houston. G 3.

9:15 A.M. Investigations of P-32 Tagged Triethylene-Thiophosphoramid in Isolation Perfusion Techniques.
D. B. ROCHLIN, Los Angeles. G 4.

9:30 A.M. A Double Isotope Derivative Method for the Assay of Progesterone.
C. A. WOOLEVER and ALAN GOLDFIEN, San Francisco. G 5.

9:45 A.M. Exhibit Break

Chairman: HERBERT C. ALLEN, JR., M.D., Houston, Texas.

10:15 A.M. Studies on the Antigenicity of Insulin with I^{131}-labeled Insulin.
ROSALYN S. YALOW and SOLOMON A. BERSON, Bronx. G 6.

10:30 A.M. Metabolic Fate of In Vivo Labeled Rat Erythrocytes.
BERGENE KAWIN and JENG M. HSU, Baltimore. G 7.

10:45 A.M. Tritiated Thymidine as an Investigative Tool in the Study of Malignant Disease in Animals and Humans.
EUGENE P. FRENKEL, CHARLES T. KNORPP and DONALD R. KORST, Ann Arbor. G 8.

11:00 A.M. Glucose Kinetics and Oxidation and the Effects of Insulin, Tolbutamide and Phenethylbiguanide (DBI) in Normal Human Subjects.
MYRON POLLYCOVE, Berkeley. G 9.

11:15 A.M. Estimation of Human Intestinal Function by Biochemical Biopsy and Uptake of Radioactive Nutrients.
TED M. BOW and RICHARD P. SPENCER, Buffalo. G 10.

11:30 A.M. The Use of Fresh $OI^{131}HA$, Purified Product, and Product with Long Shelf-Life in Renal Clearance Rate Studies in Unanesthetized Dogs.

HERMAN E. SCHMID, JR., I. MESCHAN, MOHAMMED S. NAVABPOUR, and CLAUDIUS D. WALKER, Winston-Salem, North Carolina. G 11.

11:45 A.M. The Biologic Fate of Neohydrin-Hg^{203} in Dogs and Humans.
HARRY C. MILLER, JEROLD P. GREEN, and JOSEPH LEVINE, Rochester, New York. G 12.

12:00 Noon Buffet Lunch* and Exhibit Viewing

FRIDAY, JUNE 29, 1962

1:30—2:00 Business Meeting and Election of New Officers—CRYSTAL BALLROOM

Afternoon Session—CRYSTAL BALLROOM

SESSION H

Thyroid Scanning

Chairman: WILLIAM H. BEIERWALTES, M.D., University of Michigan Hospital, Ann Arbor, Michigan

2:00 P.M. Studies of Metastatic Bone Lesions with Sr^{85}.
DAVID M. SKLAROFF, Philadelphia. H 1.

2:15 P.M. Magnetic Tape Recording of Scintillation Scan Data.
FREDERICK J. BONTE, JACK S. KROHMER, ERNEST A. ELMENDORF, STANLEY E. HODGES, and WILLIAM E. ROMANS, Dallas. H 2.

2:30 P.M. Correlation of Pre-operative Thyroid Scintigrams and Whole Organ Subserial Sections of the Thyroid Gland Following Total Thyroidectomy in 80 Patients with Thyroid Cancer.
MICHAEL IBANEZ and RAYMOND G. ROSE, Houston. H 3.

2:45 P.M. Technetium-90, As a Biological Tracer.
P. V. HARPER, G. ANDROS, K. LATHROP, W. SIEMENS, and L. WEISS, Chicago. H 4.

3:00 P.M. Models and Photoscanning.
D. L. TABERN and G. DEAN, Highland, Illinois. H 5.

3:15 P.M. Some Effects of N-(4-Iodo-Pyrazole-Methyl)-Tetracycline in Animals.
C. D. ESKELSON, A. L. DUNN, R. E. OGBORN, and J. F. MCLEAY, Omaha. H 6.

3:30 P.M. Exhibit Break

Chairman: MONTE BLAU, Ph.D., Buffalo.

4:00 P.M. Calibration of a Slit Collimated Scintillation Counter.
JOSEPH P. CONCANNON, ROY E. SUMMERS JR., NORMAN S. WILLIAMS, and CHARLES V. MOOERS, Pittsburgh. H 7.

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*See 12:00 noon—Session B (page 169)

4:15 P.M. Anemia, Leukopenia and Thrombocytopenia Following I^{131} Therapy for Thyroid Carcinoma.
THOMAS P. HAYNIE and WILLIAM H. BEIERWALTES, Ann Arbor. H 8.

4:30 P.M. Thyroid Function Studies in the Newborn.
R. T. MORRISON, T. C. EVANS, and J. A. BIRKBECK, Iowa City. H 9.

4:45 P.M. Influence of Plasma from a Variety of Stressed Animals on I^{131} Uptake in Chick Embryos.
FRANKLIN T. BRAYER, Washington, D.C. H 10.

FRIDAY, JUNE 29, 1962

1:30—2:00 Business Meeting and Election of New Officers—CRYSTAL BALLROOM

Afternoon Session—FIESTA ROOM

SESSION I

Clinical Diagnosis

Chairman: ROBERT A. NORDYKE, M.D., Straub Clinic, Honolulu, Hawaii

2:00 P.M. Plasma Triolein—I-131 Capacity in Arteriosclerotic Heart Disease —A New In Vitro Test. I 1.
LAWRENCE W. POLLARD and GUSTAVE F. KILTHAU, San Antonio.

2:15 P.M. Simultaneous Absorption Studies of I-131-Triolein and I-125-Oleic Acid in the Differential Diagnosis of Steatorrhea.
MILLARD N. CROLL and DONALD BERKOWITZ, Philadelphia. I 2.

2:30 P.M. Utilization of Intravenously Administered I^{131} Labeled Triolein in Normal Patients and Patients with Coronary Artery Disease.
BENNETT LEVINE and HERSCHEL COHEN, Cleveland. I 3.

2:45 P.M. Measurement of the Functional Capacity of the Reticuloendothelial System (RES) in Man and Dog.
MASAHIRO IIO and HENRY N. WAGNER, JR., Baltimore. I 4.

3:00 P.M. Exhibit Break

Chairman: EDWARD A. CARR, JR., Ann Arbor, Michigan.

3:30 P.M. Tracer Studies of Reticuloendothelial System (RES) Functions.
G. V. TAPLIN, E. K. DORE, E. J. GARCIA, G. N. HADDAD, and D. E. JOHNSON, Torrance, California. I 5.

3:45 P.M. Demonstration of Hydatid Liver Cysts with Colloidal Radiogold—International Atomic Energy Agency Scanning Program in Iraq.
RALPH ADAMS, A. Y. HINDAWI, and KH. QASSAB, Iraq. I 6.

4:00 P.M. A Simple Test to Estimate the Metabolic Effects of Thyroid Hormone.
TOMMIE REDDING and PHILIP C. JOHNSON, Houston. I 7.

4:15 P.M. Placentography.
MILLARD N. CROLL and LARRY H. SHUMAN, Philadelphia. I 8.

4:30 P.M. Contribution to the Testing of the I^{131}-Triiodothyronine-Uptake by Red Blood Cells.
J. FOLDES and P. CZERNIAK, Israel. I 9.

4:45 P.M. Study of the Liver Using Labeled PVP.
P. CZERNIAK, H. BANK, and S. EDELMAN, Israel. I 10.

SATURDAY, JUNE 30, 1962 *Morning Session*—CRYSTAL BALLROOM

SESSION J—Renograms

Chairman: WELBY NEWLON TAUXE, M.D., Rochester, Minnesota

9:00 A.M. Use of Renogram in Renal Shut Down Following Vascular Surgery.
ARTHUR BEALL and PHILIP C. JOHNSON, JR., Houston. J 1.

9:15 A.M. The Radiohippuran Renogram: Enhanced Reproducibility by Changes in Collimation, Kidney-crystal Distance and Patient Position.
ROBERT A. NORDYKE, Honolulu. J 2.

9:30 A.M. Improved Renal Vascular Evaluation in Hypertension by Means of a Modified I-131 Renogram Method.
WILLIAM E. WHITE, Kansas City, Missouri. J 3.

9:45 A.M. Four-channel Magnetic Tape Recording and Digital Integration Analysis of Radio-hippuran Renal Function Tests.
G. J. HINE, M. H. FARMELANT, B. A. BURROWS, and J. A. CARDARELLI, Boston. J 4.

10:00 A.M. Exhibit Break

Chairman: GEORGE V. TAPLIN, M.D., University of California, Los Angeles.

10:30 A.M. Results of a Standardized Hippuran Renogram Review of Two-Hundred and Fifty Cases.
ROBERT C. MEADE and DONALD A. FRANKLIN, Milwaukee. J 5.

10:45 A.M. Correlative Clinical Studies with the Hippuran Renogram.
WILLIAM G. BATTAILE, HECTOR J. SALAZAR, and OSCAR B. HUNTER, JR., Washington, D. C. J 6.

11:00 A.M. An Approach to the Standardization of the Isotope Renogram.
W. NEWLON TAUXE, Rochester. J 7.

11:15 A.M. Current Radiorenocystogram Interpretations.
E. K. DORE, D. E. JOHNSON, G. N. HADDAD, and G. V. TAPLIN, Torrance, California. J 8.

11:30 A.M. Renocystograms and Intravenous Pyelograms.
G. V. TAPLIN, E. K. DORE, D. E. JOHNSON, T. T. TAN, and G. N. HADDAD, Los Angeles and Torrance, California. J 9.

11:45 A.M. The Radioisotopic Renogram in Renovascular Hypertension.
JAMES L. QUINN, III, Winston-Salem. J 10.

SATURDAY, JUNE 30, 1962

Morning Session—FIESTA ROOM

SESSION K

Activation Analysis

Chairman: RICHARD E. OGBORN, M.D., Omaha, Nebraska.

9:00 A.M. Some Applications of Activation Analysis in Medicine.
RICHARD E. OGBORN, Omaha. K 1.

9:15 A.M. High Speed Activation Analysis Systems for the Analysis of Biological Materials.
R. E. WAINERDI, D. GIBBONS, and L. E. FITE, College Station. K 2.

9:35 A.M. Specific Problems in Neutron Activation for Trace Metal Analysis in Human Serum.
THEODORE FIELDS, E. KANABROCKI, E. KAPLAN, and S. BRAR, Argonne, Illinois. K. 3.

9:55 A.M. Determination of Mg. Mn. Zn and Copper in Human Blood by Activation Analysis.
W. F. BETHARD, R. A. SCHMITT, and D. OLEHY, San Diego. K 4.

10:15 A.M. Activation Techniques with a Portable 14 Mev Neutron Source.
HOWARD I. OSHRY, Houston. K 5.

10:30 A.M. The Armed Forces Radiobiology Research Institute.
JAMES T. BRENNAN, Bethesda, Maryland. K 6.

10:45 A.M. Computers in Activation Analysis.
BARNEY T. WATSON, Omaha. K 7.

10:55 A.M. The Use of a Nuclear Reactor in Activation Analysis.
ALAN J. BLOTCKY, Omaha. K 8.

11:05 A.M. Application of Activation Analysis to Various Trace Elements.
ARTHUR L. DUNN, Omaha. K 9.

11:15 A.M. Discussion.

12:00 Noon Last intermission for viewing exhibits.

SATURDAY, JUNE 30, 1962

Morning Session—TERRACE ROOM

SESSION L

Nuclear Medical Technicians

Chairman: ERVIN KAPLAN, M.D., V. A. Hospital, Hines, Illinois.

A full session will be devoted to the special interests of nuclear medical technicians. Papers dealing with instrumentation, techniques and laboratory procedures will be presented. All members and guests are urged to invite their technicians to attend the entire meeting and this session in particular.

Papers to be Read by Title

The Rate of Incorporation of P-32 Adenine Nucleotides of Erythrocytes from Normal and Schizophrenic Subjects. (T 1.)*

Joseph Bernsohn, James T. Gustod, Alexander P. Remenchik, and Peter J. Talso, Hines, Illinois.

The Long-Term Component of Sr Turnover in Man. (T 2.)

S. H. Cohn, H. Spencer, J. Samachson, and J. S. Robertson, Upton, Long Island.

Radioisotope Liver Coefficients, Using the Liver Scintillography. (T 3.)

P. Czerniak, Tel-Hashomer Hospital, Israel.

A Method for Studying Fe Absorption Using Ferrous-59 Sulfate Tablets. (T 4.)

Miguel A. Escobar, Alessandro Emanuell, and Frank E. Trobaugh, Chicago.

Experimental Study of a Specific Emotional Stress on Hyperthyroid Patients. (T 5.)

Glenn W. Flagg, Los Angeles.

The Effects of Certain Drugs on the Uptake of T3 by Erythrocytes. (T 6.)

Walter DiGiulio, Moulai Benmiloud, and George E. Thoma, St. Louis.

The Radioactive Phosphorus Test in Ophthalmology. (T 7.)

Bernard Goldberg, David Tabowitz, Gerald B. Kara, Saul Zavell, and Romeo Espiritu, New York.

Large Particles of Yttrium-90 to Treat Advanced Cancer. (T 8.)

Edgar D. Grady, Walter Sale, and Luther C. Rollins, Atlanta, Georgia.

Factors Influencing Triiodothyronine-Resin Binding. (T 9.)

C. Hland, M. Ervin, S. Guggenheim, and H. Elrick, Denver.

Study of T_3 and T_4 Binding to Glass and Electrophoretic Filter Paper Using a Dis-equilibrated Dialysis Technique. (T 10.)

John J. Imarisio, Joseph Greco, and Ervin Kaplan, Hines, Illinois.

Sulfur-35 Therapy of Mycosis Fungoides. (T 11.)

R. R. Lund and R. G. Davis, Bethesda.

The Uses of Kr-85. (T 12.)

R. J. Sanders, Denver.

Dilution Studies of K-42 Na-22 and Tritium in Familial Periodic Paralysis. (T 14.)

Peter J. Talso and Michael F. Glynn, Chicago.

Major Arterial Visualization Utilizing Right Atrial Injection and RISA Circulation Time. (T 15.)

Carl L. Williams, Timothy Takaro, and Stewart M. Scott, North Carolina.

Technical Problems from Employment of Erythrocytes As the Receptors in the Measurement of Unsaturated Thyroid-binding Globulin. (T 16.)

George E. Thoma, Walter DiGiulio, and Paul Weinhold, St. Louis.

The Compound Positron Detector—A Feasibility Study. (T 17.)

W. Paul, Toronto.

**Letter and number in parenthesis following each title in the Program refers to the corresponding abstract. The abstracts have been arranged by Session and by order of presentation, and appear in the special convention issue of* The Journal of Nuclear Medicine *(May, 1962, issue).*

B 1.** ***Tagged Isomers and Analogues of Thyroxin Transmission Across the Human Placenta. **J. E. Kearns and Herbert Philipsborn (Evanston Hospital, Evanston)**

In 1956 Grumbach and Werner reported in an editorial in the Journal of Clinical Endocrinology and Metabolism, the transfer of thyroxin across the human placenta. We have repeated this experiment and not only used levothyroxin but dextrothyroxin, triiodothyronine, and dextrotriiodothyronine.

Twelve mothers at term were induced for labor. Some of the mothers were given iodine previous to the oral administration of the tagged drugs. We found that there was no difference in the transfer. The mothers were given 50 microcuries at varying time intervals (2 to 8 hours) previous to delivery. Only one dose was given at the time of delivery and a blood sample was taken from the mother and cord blood (the fetal circulation of the hormone). The values for the transmission of the various isomeres and analogues of thyroxin were about equal. Those of T^3 were slightly higher than T^4.

In an attempt to see if these substances were transferred as themselves, paper chromotography was done. We found that in most instances, due to the small dose of tagged drug, there was insufficient amount of radiation on the chromatograph to make recordings. However, we have sufficient evidence that it is the same as the drug administered.

Trying to find out why we had quantitative differences between maternal and cord blood, a study of protein binding factor in the mother and cord blood was done. It was found that there was considerable difference between the cord blood and that of the mother.

In an effort to make further studies of these drugs to see if there was any difference, we show the compartments into which they fall in normal humans over the age of 50.

Studies on the excretion of these drugs through biliary and jejunal fistulae were done.

B 2. ***1200 T-3 Procedures.*** **Bruce Sodee (Washington, D. C.)**

B 3. ***Comparative Thyroid Function Studies with the Resin T-3 Test.*** **Francis Foeckler, Nellie May Bering, Joanne Siragusa, and Oscar B. Hunter, Jr. (Oscar B. Hunter Memorial Laboratory, Washington, D. C.)**

In June 1961 Scholer reported an in vitro thyroid function test using a basic ion-exchange resin labeled with I^{131}-l-triiodothyronine. We compared this method with the Hamolsky red cell technique on 200 patients and found excellent correlation in most cases. Thereafter we adopted the resin method as our routine procedure for T-3 determination and since then have performed well over 1000 tests using this method. However, the presence of large amounts of both organic and inorganic I^{131} in the plasma of therapy patients quite often invalidates the results of the resin method, and in these cases the Hamolsky red cell technique must still be used. Plasma from patients with liver disease often gives results in the hypothyroid range, while whole blood from these cases shows a red cell uptake in the hyperthyroid range. With both methods the results outside the euthyroid range could be attributed to abnormal ratios of the serum proteins.

The Scholer resin technique is a rapid and usually accurate in-vitro method of determining thyroid status. It is a great time saver in laboratories where large numbers of T-3 tests must be performed daily.

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B 4. *Statistical Analysis of the "Hamolsky-RBC-T-3" Test As Compared with the "Sephadex-T-3" Test.* **J. L. Rabinowitz and Bernard Shapiro (Radioisotope Service, Veterans Administration Hospital and Biochemistry Department, University of Pennsylvania; and Research Laboratory, Department of Radiology, Albert Einstein Medical Center, Southern Division; Philadelphia)**

Reports have now been received from various institutions where both of these thyroid function tests are carefully under study. With a total of over 500 different patients having been evaluated by: a) 24 hour I-131 uptake, b) PBI, c) History and physical, d) the Hamolsky-RBC-T-3 test, and e) the Sephadex-T-3 test, the obtained correlations are: 1) Very good general agreement between the various tests; b) between the *in vitro* tests the agreement was over 85% in the euthyroid range, 90% in the hyperthyroids, and 78% for hypothyroids. Additional data is being compiled to bring the total evaluated number of patients to 1000.

Current work is in progress for the adaptation of this test for the evaluation of thyroid function of small animals. Parallel biochemical investigations continue on the mechanism of T-3 uptake by specific sera protein sites.

B 5. *Liver Uptake of Rose Bengal I^{131} in Gastrointestinal Bleeding.* **Ismael Mena, Vicente Valdivieso, Catalina Maggiold, and Enrique Montero (The Catholic University, Santiago, Chile)**

It has been reported that retention of bromsulphalein (BSP) is abnormally high in 15 percent of patients with acute digestive bleeding and normal liver function. This study was undertaken to evaluate liver function in acute hemorrhage, and to rule out bleeding due to esophageal varices.

Twenty-seven patients with gastroduodenal ulcer or acute gastritis without liver disease, and 10 cirrhotic patients with acute bleeding were studied. The uptake of Rose Bengal I^{131} was measured. Cardioportal circulation time was also measured to determine the existence of portal hypertension.

Twenty-six of 27 patients with acute bleeding due to gastroduodenal ulcer or gastritis showed a normal uptake of Rose Bengal I^{131} and cardio portal circulation time. One patient had an abnormally low uptake of Rose Bengal I^{131}, and returned to normality one week after cessation of bleeding. In 10 cirrhotic patients the uptake of Rose Bengal I^{131} was consistently low. The values for cardioportal circulation time showed considerable variation and were of limited diagnostic value. It is concluded that Rose Bengal I^{131} uptake is normal in acute anemia due to bleeding, and may be of diagnostic value in management of this problem.

The difference between findings of others using BSP and the results with Rose Bengal I^{131} in the present study may be due to the small amount of dye needed for the tracer study.

B 6. *The Use of 24 Hour Blood Levels of I^{131}-labeled Rose Bengal Dye in the Differential Diagnosis of Jaundice.* **Norman B. Ackerman and Arthur S. McFee (Department of Surgery, University of Minnesota Medical School, Minneapolis)**

Rose bengal dye is removed from the blood by the parenchymal liver cells and is excreted rapidly through the biliary system into the intestines. Essentially no trace of the dye can be found in the blood after 24 hours. Where moderate hepatocellular damage is present there is usually enough function remaining to clear the blood by 24 hours. However if there is a complete obstruction of the biliary tract, small quantities of rose bengal can still be detected in the blood at 24 hours. If obstruction is only partial, there is usually enough flow of dye to cause complete blood clearance by 24 hours.

The identification of complete biliary obstruction is thus possible by measuring whole blood radioactivity 24 hours after administering I^{131}-labelled rose bengal. In the adult complete obstruction is usually due to the presence of a malignant tumor, such as cancer of the bile duct or head of the pancreas. Benign obstruction due to stricture, stenosis or stones usually produces a partial blockage. Patients with diseases of the liver and biliary tract were given 25 microcuries of I^{131}-labelled rose bengal intravenously and 24 hours later 2 cc. of venous blood was withdrawn. Radioactivity of the blood was counted in a well scintillation counter. Patients with biliary tract cancer had radioactive blood levels ranging from 82 to 531 cpm., while patients with benign disease had levels of 13 to 52 cpm. Preliminary studies on infants using 0.5 microcuries/kg. body weight have demonstrated elevated 24 hour blood levels of the dye in the presence of complete biliary atresia.

B 7. *A Comparison of Thyroid Function Tests: the 6- and 24-hour Thyroidal Uptake, T-3 Red Cell Uptake, T-3 Resin Uptake, Reflex Recording and the PBI.* **R. A. Nordyke, A. M. Brault, and A. Tonchen (Straub Clinic, Honolulu)**

The purpose of this study is to compare the T3-I^{131} red cell and resin uptake tests with standard tests of thyroid function for the diagnosis of hyperthyroidism in a large clinic practice. Six hundred forty patients were examined, of whom 97 (15.2%) had hyperthyroidism. The final diagnosis was made on the basis of a history and physical examination and the following tests as applicable: T-3 red cell uptake, T-3 resin uptake, PBI^{127}, thyroidal I^{131} uptake at 6 and 24 hours, reflex relaxation recording and the T-3 suppression test (Werner). The results were as follows:

	Test # patients	*# hyper-thyroid*	*Range in normal subjects (2 S.D.)*	*Range in hyperthyroid patients (2 S.D.)*
T-3RCU (%)	406	58	14.2 ± 3.7	21.0 ± 6.0
T-3 Resin uptake (index)	119	13	1.00 ± 0.12	1.53 ± 0.23
PBI^{127} (μgm%)	180	37	7.4 ± 3.4	10.6 ± 4.1
Thyroidal UT 6 hrs. (%)	558	82	12.5 ± 9.5	56 ± 35
Thyroidal UT 24 hrs. (%)	626	70	22 ± 20	62 ± 30

The *PBI^{127}* was discarded early in the study because of its failure to discriminate among diagnostic categories. This was particularly evident in elevated results, often due to iodine contamination from foods common to the Hawaiian population. The *T-3 red cell uptake* (Homolsky) discriminated well when the result was over 18% (no normal patient was over 19.2%), but 24% of the hyperthyroid patients fell within the normal range. The *thyroidal uptakes at 6 and 24 hours* discriminated well when the results were high (over 30 and 45 respectively), but about 25% of hyperthyroids fell within normal limits at each time period. The *T-3 resin uptake* (Sterling) gave the clearest discrimination of diagnostic categories. To date there has been no overlap between normal and hyperthyroid patients.

The *in vitro* T3-I^{131} tests are clearly superior to the PBI^{127} in simplicity and reproducibility and are not invalidated by iodine contamination. We now rely on the T3-I^{131} resin uptake in combination with the thyroidal uptake at 6 and/or 24 hours. The T-3 suppression test (Werner) is used as a final arbiter in equivocal cases.

B 8. *Radioiodine-123.* WILLIAM G. MYERS and HAL O. ANGER (Ohio State University Health Center, Columbus, and Donner Laboratory of Biophysics and Medical Physics and Lawrence Radiation Laboratory, Berkeley)

Iodine-123 has physical properties that make it advantageous over the other twenty radioisotopes of iodine for *in vivo* measurements.

Calculations indicate radiation exposures will be less than 5% as great when I-123 is substituted for I-131, in procedures where radioiodide ion is administered. This reduction stems chiefly from two properties: 1) I-123 emits *no* β-particles, per se, like I-131 does; 2) The ~14-hour half-life of I-123 is only 7% that of I-131. However this half-life is adequate for most diagnostic procedures.

Calculated narrow-beam half-thickness in water for its 159-kev γ-ray is 4.6 centimeter which provides ample penetration.

Calculated narrow-beam half-thickness of 159-kev photons in sodium iodide is 0.35 centimeter. A detector with a one-half inch thick-crystal efficiently absorbs the γ-rays as well as the 28-kev (average) x-rays that accompany the decay of I-123.

Calculated narrow-beam half-thickness in lead is 0.037 centimeter. Conveniently light detectors are readily made highly directional. Shielding protection is simplified in comparison with I-131.

Iodine-123 was produced readily by the Sb^{121} $(He^4,2n)I^{123}$ reaction when thick targets of antimony powder enriched to 99.4% Sb-121 were bombarded with 30-Mev He-4 ions in the 60-inch Crocker cyclotron. There was only slight contamination with 4.5-day I-124. When natural antimony (57.25% Sb-121, 42.75% Sb-123) was similarly bombarded, the high-energy γ-rays from I-124 produced from the Sb-123 became troublesome by the third day.

Experiments are projected to generate I-123 in Curie quantities, and free of other radioisotopes, by a method suggested by Professor Isadore Perlman: $_{52}Te^{122}(He^4,3n)_{54}Xe^{123}$ (continuously pumped off) $\xrightarrow{\text{1.8 hour } \beta^+}$ $_{53}I^{123}$. The $Te^{123}(p,n)$ I^{123} and $Te^{124}(p,2n)I^{123}$ reactions might also prove suitable.

B 9. *The Use of I-125 in Clinical Nuclear Medicine.* LESTER M. LEVY, TERESITA T. ESTRELLADO, OKOGBUE OKEZIE, and H. S. STERN (Division of Nuclear Medicine, The Long Island Jewish Hospital, New Hyde Park, Long Island)

Through the courtesy of Dr. H. Stern of the Squibb Institute we have had the opportunity of exploring several forms of I-125.

The I-125 could be readily counted with convention instrumentation and readily determined in the presence of I-131 by means of unmodified pulse height analysis equipment, after a 10% level of "cross-talk" from I-131 was eliminated.

A. I-125 tagged human serum albumin. Simultaneous I-125 and I-131 HSA blood volumes were performed. In one such experiment, aliquots from a single batch of I-125 HSA were compared to fresh samples of I-131 HSA (renewed every two or three weeks) over a ten week period. The simultaneously determined blood volumes were invariably within statistical counting error of each other demonstrating no appreciable deterioration of the I-125 HSA over at least a ten week interval. The mean absolute percentage deviation of the I-125 HSA blood volume with respect to the I-131 HSA blood volume was 1.66% in 29 successive patients.

B. I-125 tagged oleic acid. Simultaneous I-125 and I-131 oleic acid absorption studies were performed assaying both blood and fecal specimens. Results were within counting statistic error. This is a necessary preliminary to simultaneous triolein-I-131 and oleic acid I-125 studies which will afford considerable savings of hospital bed time and specimen collection and processing. These are now under way.

C. Sodium-iodide-125 studies. A series of simultaneous Na I-131 and Na I-125 thyroid uptakes and scintiscans were performed, using a wax phantom and 0.5 cm. wax cover over a

25 ml. plastic flask as the standard. Thyroid uptake values with I-125 ranged from 60-75% of those obtained with I-131. This may be due to a combination of poor phantom match and variable depth of thyroid. This problem is under study. Scans with I-125 gave somewhat better resolution than those with I-131 using a 2×2 inch crystal and 19-hole focusing collimator. However, counting rate on a microcurie basis was less for I-125 probably because of better collimation and less leakage through lead septa.

I-125 was especially useful in a second scan after a previous baseline study such as after triiodothyronine suppression or T.S.H. stimulation. By this means previous isotope could be "screened out" by pulse height selection and only the new thyroid function visualized. Several examples of information revealed by I-125 but not by I-131 simultaneous scans will be presented.

D. Studies with other forms of I-125 and with I-125 as a long-lived "reagent" are under way.

The studies already concluded demonstrate that I-125 has definite clinical utility although certain problems remain to be resolved.

B 10. ***The Cobalt-60 Vitamin B-12 Test—The Interpretation of Borderline Values.*** **Ben I. Friedman, Eugene L. Saenger, and Robert Ruskin (Radioisotope Laboratory, Cincinnati General Hospital and Departments of Medicine and Radiology, University of Cincinnati College of Medicine, Cincinnati)**

The interpretation of borderline values has been most perplexing since Schilling originally described the Vitamin B-12 Co-60 urinary excretion tests as a method to evaluate absorption of vitamin B-12. We, too, have been concerned and therefore have critically analyzed this "gray zone" as seen in over 250 studies since 1955.

Twenty-four patients have been observed with one or more values in our "gray zone" of 2.9% to 7.7% excretion. Eight patients had had subtotal gastrectomy with gastrojejunostomy. Only one of these patients presented with megaloblastosis. Clinically eight patients had been diagnosed as having pernicious anemia. Other diagnoses found in this group were sprue, Felty's syndrome, hyperplastic refractory anemia, malnutrition with anemia and neurological disease with posterior column abnormality. Only one patient with renal disease manifested borderline results, but these values were clearly caused by decreased excretion rather than by decreased absorption.

Patients who have results falling in the "gray zone" do have alteration in the absorption of vitamin B-12, but to a lesser degree, than those patients with values in the pernicious anemia range. We have been impressed that these "gray zone" values are seen in patients who have the substrate for megaloblastosis or some other form of anemia. The difficulty with absorption of vitamin B-12 in patients who have had subtotal gastrectomy and gastrojejunostomy is well worth reemphasizing. The concept of a "gray zone" is a real one and should not be discarded as representing a false compartmentalization.

C 1. ***Ca^{47} Studies in Man.*** **E. Miller, C. J. Hlad, Jr., M. Ervin, and H. Elrick (Veterans Administration Hospital and University of Colorado School of Medicine, Denver)**

Studies of calcium utilization, using radioactive Ca^{47} have been carried out in 57 subjects (47 normal or with disorders unrelated to calcium metabolism, and 10 with diseases often associated with abnormal calcium metabolism). Doses of 0.5 to 1μc/kg. body weight of Ca^{47} were used. Diets varied from low to high calcium content. Radioactive assay of samples for energies above 0.2 Mev. eliminated the contribution of Sc^{47}, a daughter of Ca^{47}.

In the 39 subjects who had complete 72 hour urine collections, the mean Ca^{47} excretion was 4.1% ± 2.4% of the administered dose. There was no correlation between Ca^{47} excretion and stable calcium excretion. The 10 patients with diseases of calcium metabolism showed excretion patterns similar to those observed in normals.

Fecal Ca^{47} showed wide variations which were unrelated to dietary calcium; e.g., 3 normal volunteers on a 6 day low calcium diet, given 0.5 μc/kg. Ca^{47} + 90 mg. of carrier calcium, excreted 1.3, 31.8, and 57.9% of the Ca^{47} respectively in the stools. The 10 patients with diseases of calcium metabolism showed a similar wide variation. In 33 subjects with complete 72 hr. urine and fecal collections, total Ca^{47} recovery ranged from 6.2 to 76.5%.

In 5 normal patients given carrier free Ca^{47} by constant I.V. infusion, plasma Ca^{47} increased in a shallow smooth curve throughout the 120 min. infusion. The 72 hr. excretions ranged from 4 to 11.6% in the urine and from 2.6 to 11.8% in the feces.

Preliminary results using the whole body counter to measure Ca^{47} body retention will also be reported.

C 2. *Some of the Factors Affecting Interpretation of Studies Employing a Single Intravenous Injection of Ca^{45}.* **Richard Goldsmith, Mildred J. Wiester and Wendell M. Riddell (Radioisotope Laboratory, Veterans Administration Hospital, Cincinnati)**

There is a considerable amount of data now available concerning the fate of Ca^{45} after a single intravenous injection of labelled calcium into a living subject. Quantitative estimates of various reactions involving the metabolism of bone have been calculated on the basis of such information. The present report concerns factors to be considered in the evaluation and interpretation of such estimates. Reproducibility of data was examined with two identical studies performed three months apart on the same patient. Blood, urine and stool specific activity of calcium was measured. The radioactivity disappearance slopes for blood, the miscible calcium pool size and similar calculated values were practically identical for the two studies. The effect of diet was examined in another patient who was studied while on a 200 and again a 2000 mg. daily intake of calcium. The parameters first noted differed in the two studies: There was more apparent penetration of the label into body stores of calcium on the higher calcium intake. *In vivo* and *in vitro* studies were also performed to investigate the homogeneity of labelling of blood calcium under the circumstances present during such studies. The *in vitro* data suggested that the complexed-but-diffusible fraction of the blood calcium was not labelled as quickly as was the rest and that there was a time lag before homogeneous blood labelling was achieved.

C 3. *Na-22 Secretion in Sweat.* **H. W. Weigel, J. Parsons, C. J. Hlad, Jr., E. Miller, and H. Elrick (Veterans Administration Hospital and University of Colorado School of Medicine, Denver)**

A new technique for studying the secretion of sodium in sweat has been developed. An oral dose of 0.15 μc. of Na^{22} per kg. of body weight was administered. Eighteen to 21 hours later, sweating was stimulated on the forearm by pilocarpine nitrate applied by ionophoresis for a 10 min. period. Immediately thereafter, a sweat sample was collected for 30 min. on a special absorbent pad. Samples for serum Na^{22} and sweat chloride (Schales') were also obtained. Na^{22} secretion in the sweat was expressed as a ratio of the concentrations (R): sweat Na^{22}/serum Na^{22}.

Studies were carried out in 77 patients. Fifty normal subjects showed a mean R value of 25 (range 8 to 41) and a mean sweat chloride of 18.8 mEq/L (range 1 to 58). Four patients with fibrocystic disease of the pancreas showed R values from 57 to 85, and sweat chlorides from 74 to 129 mEq/L. Twenty patients with chronic lung disease had a mean R value of 34 (range 9 to 75) and a mean sweat chloride of 39 mEq/L (range 10 to 115). Three subjects with chronic pancreatitis had R values which ranged from 17 to 31 and chloride values which ranged from 11 to 18.

The physical characteristics of Na^{22} (long half-life and high counting efficiency) make it ideal for routine use. Radio-assay of a sweat soaked pad can be performed quickly, accurately, and directly in a well type scintillation counter. The technique therefore has advantages over

chemical methods. It appears to be a useful diagnostic procedure for cystic fibrosis of the pancreas. The results also suggest that some patients with chronic bronchopulmonary disease may have a form of cystic fibrosis of the pancreas.

C 4. *The Relative Flow Rates of Red Cells and Plasma in Hypotensive Dogs.*

Milton G. Crane, John E. Holloway, Ralph Adams, and Ivor C. Woodward (Loma Linda University, Los Angeles)

The relative flow rates of red cells and plasma were measured in the hepatic portal circulation of the dog by injecting a mixture of Cr^{51}-labelled red cells and I^{131}-labelled plasma into the freely flowing portal vein circulation. The mean transit times (MTT), flow rates, and volume of dilution of each phase in the hepatic venous blood were calculated from the isotope dilution curves obtained from the simultaneous counting of Cr^{51} and I^{131} by differential pulse height analysis.

In sixteen tests of the hepatic portal circulation the average MTT for plasma and red cells was 19.89 ± 8.09 and 13.20 ± 5.54 seconds respectively.

Comparative values for other vascular beds in the dog are as follows. In twenty tests of the pulmonary capillary bed the average MTT for plasma and red cells was 8.77 ± 1.65 and 8.44 ± 1.38 seconds respectively. In twenty tests of the leg circulation the average MTT for plasma and red cells was 15.51 ± 9.61 and 13.91 ± 8.76 seconds respectively. In ten tests of the cerebral circulation the average MTT for plasma and red cells was 16.5 ± 7.00 and 14.30 ± 5.94 seconds respectively.

The MTT of plasma was significantly greater ($P < 0.01$) than the MTT of red cells in all four vascular beds. In the four different vascular beds mentioned above the ratios of the regional hematocrits to the large vessel hematocrits were 0.73 ± 0.06, 0.97 ± 0.04, 0.89 ± 0.07, 0.90 ± 0.02 in the same order as above.

In every hepatic portal circulation test the MTT of plasma was greater than that of red cells and was significantly greater ($P < 0.01$) than for the three other vascular beds. This suggests that the blood channels in the portal circulation are smaller in diameter than those of the other regional circulations tested.

This investigation was supported by research grant H-2195 from the National Institutes of Health, U.S. Public Health Service.

C 5. *Use of a Whole Body Counter in Turnover Studies of Ca-47 and Fe-59.*

Thornton Sargent, Myron C. Pollycove, John A. Linfoot, and John H. Lawrence (Donner Laboratory, University of California, Berkeley)

A Whole Body Counter by virtue of its great sensitivity of gamma emitting isotopes within the human body makes possible turnover studies not previously practical. The percent absorption of a small oral dose of an isotope can be accurately measured without blood, urine or stool collections. Four patients presenting symptoms of intestinal malabsorption have been studied for absorption of Co^{57}, Fe^{59} and Ca^{47}. Absorption of iron has been studied in patients with a variety of types of anemia, some of whom were found to have impaired iron absorption. Although standard tests for blood in stools had been negative, some patients presented the complication of blood loss, which was accurately and easily determined by periodically measuring the decrement of total body radioiron.

In a patient with congenital hemorrhagic telangiectasia it was possible to measure the turnover of iron in a compartment believed to represent myoglobin and heme enzymes. The turnover of Ca^{47} was determined in normal subjects, in patients with acromegaly before and after treatment, and in patients with cancer with an without bone involvement. Significant differences in turnover which may be useful in diagnosis were found in patients with the pathological bone involvement.

C 6. *The Clearance of Labeled Particulate Matter from the Human Tracheo-Bronchial Tree as Determined by External Monitoring.* ANGELO TOIGO, JOHN J. IMARISIO, HUNTER MERMALL and M. LEPPER (Medical and Radioisotope Services, Veterans Administration Hospital, Hines, Illinois)

One of the prime defenses of the normal lung against foreign particulate matter is the beating action of the ciliated epithelium which continuously moves a thin mucous blanket overlying the tracheobronchial mucosa toward the mouth. Foreign particulate matter entering the tracheobronchial tree is deposited on the mucous blanket and removed from the tracheobronchial tree. The ability of the lung to remove foreign particulate matter might be measured if a suitable particle labeled with a radioisotope were deposited on the ciliated epithelium and its rate of removal from the lung determined. Carbon was chosen for this study and by a process of air tumbling and agitation carbon particles were obtained whose mean particle diameter was between 50 and 70 micra. Radioactive sodium I-131 was then adsorbed onto the carbon particles.

By means of a suitable apparatus the labeled carbon particles were delivered by inhalation to the patient's lung. The patient was then placed in front of a collimated scintillation detector connected to a count rate, scaler, recorder system. This device measured the time rate of change of I-131 activity over the bifurcation of the trachea.

Two groups of patients were studied—normal patients without lung disease and patients with chronic lung disease. The normal patients are characterized by a low initial count, a rise to a peak and a fall to a plateau. The time taken to arrive at the plateau was 120 minutes. The abnormal patient rises to a somewhat lower peak and takes 220 minutes to arrive at the plateau. The inference is that pulmonary clearance of labeled particles is much slower in patients with chronic lung disease.

C 7. *Factors Influencing the Incorporation of Radioactive Halogenated Pyrimidines into the DNA of Normal and Neoplastic Tissue* In Vivo. JOSEPH P. KRISS and LASZLO REVESZ (Stanford University School of Medicine, Palo Alto)

The halogenated analogs of thymidine, 5-iododeoxyuridine (IUdR) and 5-bromodeoxyuridine (BUdR) are to some extent incorporated in place of thymidine into the DNA of mammalian cells, *in vitro* and *in vivo*. In Addition, 5-bromodeoxycytidine (BCdR), may be deaminated by certain tissues to BUdR, and thence incorporated. The extent of incorporation into DNA of 5-iododeoxycytidine (ICdR), possibly via the analogous intermediate formation of IUdR, is under study.

Using Br^{82}-BUdR and Br^{82}-BCdR, the metabolic fate of these compounds has been studied and compared in rats, mice, and man. After intravenous administration of BUdR, a large fraction is rapidly degraded in the liver; with the formation of bromouracil and liberation of bromide. Most of the remainder is incorporated into DNA with a tissue distribution similar to, but quantitatively about 1/4 that of thymidine. In the rat BCdR is degraded more slowly than BUdR, neither bromocytosine nor bromouracil being detected as degradation products. After BCdR injection, the marrow concentration of radioactivity was disproportionately high compared to the findings with BUdR, which finding suggests that such marrow activity is the consequence of the presence of deoxycytidylate deaminase in this organ. Following incorporation of Br^{82} by Ehrlich ascites cells after intraperitoneal administration of Br^{82}-BUdR and Br^{82}-BCdR to mice, the radioactive label was conserved during neoplastic cellular multiplication for at least 4 successive generations. Using I^{131}-and I^{125}-ICdR, it has been shown that this compound is degraded in the rat at a rate similar to that of BCdR. Incorporation of the label into DNA is quantitatively less than that which follows Br^{82}-BCdR injection. The use of these gamma emitting radioactive compounds introduces the possibility of studying DNA synthesis in various normal and neoplastic tissues by external detection techniques. The major problems concerned with selective tumor localization of the compounds will be discussed.

C 8. *Passage of Fe-labeled Erythrocytes into the Systemic Circulation.* F. Keith Bradford and Philip C. Johnson, Jr. (Department of Neurosurgery and Medicine, Baylor University College of Medicine, Houston)

Studies by others have shown that India Ink particles and P-32 labeled erythrocytes will transfer across peritoneal and subarachnoid serosal linings. We have extended these observations to other cavities by using Fe-59 labeled cells because unlike P-32 the radioactivity will not diffuse from the cells.

Fresh whole canine blood containing Fe-59 labeled erythrocytes was injected into serosal lined cavities of dogs. Peripheral blood specimens were obtained at various intervals thereafter. By calculating total red cell mass it was possible to determine the percentage of the injected erythrocytes which are transferred intact in the peripheral blood. Control experiments ruled out hemolysis and resynthesis of hemoglobin as the reason for the appearance of Fe-59 containing erythrocytes in the blood. A summary of the results obtained is as follows: about 50% of the erythrocytes can be recovered in the peripheral blood 24 hours after injections of 20-50 ml of blood into the peritoneum, pleura, pericardium and subarachnoid space. About 23% of the erythrocytes contained in 0.7 ml of blood and injected into the anterior chamber of the eye can be recovered in the peripheral blood. Only 2% of the erythrocytes appear after injection into the knee joint, and only 1% after intramuscular injection. The transfer of these cells occurs by lymphatic channels and movement of the membrane as occurs in the pericardium increases the rate of this transfer. These studies demonstrate the permeability of these membranes to particles as large as erythrocytes, and show that lymphatic transfer of erythrocytes does not destroy them. These results suggest also that the pressure within these cavities is greater than that of the interstitial spaces resulting in a continuous transfer of fluid across these membranes.

C 9. *The Identification of True Chylous Effusions with Radioiodinated Trioleate.* Phillip Rubin, Alvin Ureles, Charles Sherman, and Jerold Green (Department of Radiation Therapy and Radioisotopes and the Department of Surgery, University of Rochester School of Medicine and Dentistry, Rochester, New York)

The differentiation between chylous (obstructive) and "chyliform" (degenerative) effusion is frequently difficult since in both the turbidity is secondary to emulsified fat and the concentrations of cholesterol and lecithin are not always characteristic. Pseudochylous effusion, though containing little or no fat, may have a similar turbidity due to high concentrations of cholesterol, lecithin, or highly dispersed albumin and requires differentiation from the obstructive type.

In two patients with true chylous effusions, the presence of a mechanical lymphatic obstruction was readily demonstrated by the oral administration of 100 μc of I 131 labelled glycerol trioleate with subsequent periodic sampling of blood and effusion. Serial counts of the aspirated radioactivity from each effusion and blood over a period of 24 hours following the oral administration of radioiodinated trioleate revealed a definite increase in activity in the true chylothorax as opposed to blood levels whereas the activity of malignant effusions was below blood levels. Patients with malignant effusions, chyliform or sanginous are also being studied.

Experimental studies elaborating the use of radioiodinated trioleate for the purpose of characterizing true chylous effusions will be presented.

The therapeutic implications in malignant disease are to treat the mediastinum in cases of true obstructive chylous thorax to clear the effusion. In chyliform malignant effusions, the plan should be directed to treat the pleural space with radioisotopic or chemotherapeutic instillations.

C 10. ***Determination of Blood Volume Distribution by Whole Body Counting.*** **GUNNAR SEVELIUS, DANIEL R. PATRICK, BETTY O'CONNOR, ELAINE PATRICK, and BILL COLEMAN (Veterans Administration Hospital, Oklahoma City)**

With 100 microcuries of radioiodinated serum albumin evenly distributed through the blood volume of the patient, a whole body count is performed. The patient is placed along a circular line in supine position. The line has a seven foot radius and is isodosical. In the middle of the circle, is placed a five by five inch un-collimated scintillation detector with the detector directed towards the middle of the patient. A three minute whole body count is proportional to the amount of blood volume seen by the detector and the amount of tracer substance used for its tagging. If a portion of the body is shielded, a second count will yield the percent of blood volume shielded. The actual total blood volume may be determined in milliliter units by standard procedure. The percent blood volume shielded times the actual blood volume, yields the amount of blood in milliliters units in the shielded portion of the body.

Model experiments show that volumes as low as 300 milliliters may be determined with good accuracy. Some clinical experience with the technique will be reported.

D 1. ***The Possibilities and Limitations of Flow Measurements by External Counting.*** **BENEDICT CASSEN (Medical Physics Section, University of California Medical Center, Los Angeles)**

The results of a complete theoretical analysis of the principles of external counting flow measurement are presented. Two main principles are called for convenience the A-principle (A for pulse area) and the T-principle (T for transit time). The possible methods of calibrating A-principle measurements are presented. The T-principle measures flow per unit volume of a flow compartment. These principles are discussed in relationship to the behavior of mixing compartments. It is shown what type of results might be expected in attempts to measure coronary insufficiencies of various types. The application of the principles to cerebral blood flow measurement possibilities and limitations is discussed. Various other diagnostic applications are considered.

D 2. ***Clinical Experience with the Coronary Flow Index.*** **HARRY BISHOP and ISMAEL MENA (Department of Radiology, UCLA Medical Center, Los Angeles; and the Department of Nuclear Medicine, Catholic University, Santiago, Chile)**

The downslope of the radioactive indicator dilution curve obtained by external monitoring over the precordium is more prolonged than the downslope of the curve simultaneously measured by direct arterial sampling.

Animal experiments show that this prolongation of the precordial downslope is not due to scatter from extra-cardiac structures and they strongly suggest that the effect is caused by the portion of the radioactive bolus which fills the coronary arteries.

Theoretical considerations suggest that if the coronary vessels behave hemodynamically as a diluting pool, rather than a series of pipes, then the fraction of the radioactive bolus traversing them might indeed produce the curve distortion that is actually observed.

The prolongation of the precordial curve may be characterized by the ratio of the exponential constants of the slopes of the arterial and precordial curves. This ratio of slopes, R, may be approximately expressed in terms of the left ventricular volume V_1, the cardiac output F_1, and the volume of the coronary vascular bed 1/2:

$$R = \frac{-\dfrac{1}{1 - \dfrac{V_1}{F_1}}}{\dfrac{V_2}{F_2}} = \frac{1}{1 - \dfrac{t_1}{t_2}}$$

where t_1 and t_2 are the transit times through the left ventricle and coronary bed respectively.

The validity of this formulation has been demonstrated by independent measurements of R and the parameters V_1, F_1, V_2 and F_2 using a hemodynamic model.

The ratio R appears to depend primarily on the rate of filling of the coronary arteries which is decreased in occlusive disease. Thus R may be used as an indication of the patency of the coronary arteries and has therefore been called the Coronary Flow Index.

D 3. *Coronary Blood Flow by Radiographic Technique, ECG and Clinical Diagnosis—A Correlation Study.* **Gunnar Sevelius, Daniel R. Patrick, Betty O'Connor, Elaine Patrick, and Bill Colemen (Veterans Administration Hospital, Oklahoma City)**

During 1962 a correlation study for evaluation of the clinical value of the radiographic technique for determination of coronary blood flow will be performed. Consecutive admissions to the Veterans Administration Hospital, Oklahoma City, will have a determination of their coronary blood flow. The reported value will be correlated with the clinical diagnosis of normal heart versus arteriosclerotic heart disease, and also with the corresponding ECG findings. At the time of the annual meeting for the society of Nuclear Medicine, we hope to have about 2000 determinations available for statistical analysis.

In a pilot study of 140 patients in six weeks, the value for coronary blood flow was correlated with a clinical diagnosis and ECG findings. The Chi-Square between CBF and ECG yielded a value of 21.593, and a similar statistical analysis between ECG and Clinical Diagnosis yielded a Chi-Square of 22.144. Both values being significant with a p value of .001.

We are enabled to carry out this large scale screening because we have a standardized extrapolation procedure. The extrapolation is based on the "rubber-band" like extension of the tracer bolus as it dilutes through the blood stream. With the "rubber-band" like extension, is meant that any one concentration level of the bolus is diluted equal. Knowing the location of a certain concentration level, the location of any other concentration level may be extrapolated. The procedure used in the study will be described in detail.

D 4. *The Coronary Index.* **Ismael Mena and Harry Bishop (Department of Nuclear Medicine, The Catholic University, Santiago, Chile; and the Department of Radiology, University of California School of Medicine, Los Angeles)**

The downslope of the precordial indicator dilution curve measured by external scintillation counting is more prolonged than the curve obtained simultaneously by direct arterial sampling.

Experiments with animals and liquid flow models have suggested that the prolongation of the heart curve downslope is due to the filling of the coronary arteries. An increased rate of filling of the coronary arteries causes greater prolongation of the heart curve downslope relative to the arterial curve. Conversely, a decrease in coronary filling rate, as occurs in coronary occlusive disease, will decrease the difference between the precordial and arterial curves. This difference is expressed as the ratio of the half periods of the downslopes, the value of which is decreased in patients with coronary insufficiency.

To avoid arterial sampling, the dilution curve obtained by external counting over the brain is substituted for the arterial curve. In a series of test subjects without evidence of coronary disease, the difference between the half periods of the brain curve and arterial curve was 8 ± 5 percent. In patients with coronary insufficiency, however, this difference tends to be increased.

The ratio of the downslopes of the externally determined heart and brain curves is a simple and rapidly determined clinical measurement. This ratio:

$$\text{C.I.} = \frac{\text{T-½ Heart Curve}}{\text{T-½ Brain Curve}}$$

appears to be influenced by the coronary circulation and, therefore, has been termed the Coronary Index.

The C.I. for subjects without evidence of coronary disease falls in the range of 1.4 to 1.8, while in patients with coronary insufficiency it falls in the range of 0.95 to 1.2.

D 5. *Cerebral Circulation Studies.* W. H. Oldendorf (U.C.L.A. Medical School, Los Angeles)

Measurements of cerebral circulation by existing methods such as the nitrous oxide or its radioactive gas modifications have told us that a considerable range exists in various clinical conditions. The complex nature of these techniques makes them unsuited to routine clinical use so that we sorely lack flow data in our studies of cerebrovascular disease, tumors, aging, and other states in which flow alterations might be expected.

Radioisotopes have been applied to this problem in several ways. They have been substituted for stable substances to make quantitative analysis of specimens simpler and safer. They have been injected into the carotid system and their rate of passage through the brain determined by external detection. Most studies, however, have involved neck-vessel cannulations making them of limited value clinically.

We have pursued a simple intravenous technique using external detection of a gamma-emitter. A bolus of this material is intravenously introduced into the systemic circulation and the first passage of this bolus through the brain is monitored by an external detection system. The brain is much better suited to such a technique than any other internal organ because of its location away from other organs containing a significant volume of blood.

A reference point (the densest point) within the bolus is observed and the time of entrance into and exit from the brain blood pool is determined. This interval is a reasonably valid indication of the mean circulation time of the brain. After determining this parameter we have, in addition, attempted to determine the static volume of the brain blood pool thus, in principle, allowing us to calculate the absolute flow per unit time.

D 6. *Pulmonary Function Studies Using Krypton-85.* Hyo H. Byun, Gesila Albrecht, George W. Holmes and Robert S. Lanauer (Cook County Hospital, Chicago)

The use of the Radioactive gases, Krypton-85 and Xenon-133 for a pulmonary function test is far less time consuming, equally as accurate and requires less cooperation on the part of the patient than any other method.

We have studied approximately 100 cases of various pulmonary diseases to date. 60 cases have been compared with conventional pulmonary function tests, which includes maximum breathing capacity, vital capacity, total lung capacity, residual volume and time vital capacity. There is very favorable correlation between our method and the conventional method.

With the radioactive gas study, we are able to differentiate between normal, obstructive or restrictive ventilatory defect, cystic changes in the lung with or without bronchial connection and various type of pulmonary emphysema.

The technique is simple and the cost of equipment not excessive.

D 7. *Radio-pulmonography: A Simple Method for Simultaneous Estimation of Individual Lung Function.* M. J. Small, W. N. Miller, G. C. Leiner, H. D. Strauss, and S. Abramowitz (Radioisotope and Cardio-Pulmonary Laboratories, Veterans Administration Hospital, East Orange)

In recent years isotopic and electronic methods have been devised for the estimation of pulmonary function without resorting to bronchospirometry. These methods do not lend themselves to ready clinical use since they employ either radioactive inert gases or photomultiplier tubes for measuring light emitted by a crystal which is excited by the passage of x-rays through the lungs. X-ray sensitive cadmium sulfide cells have also been used. In the latter electronic

methods, details of instrumentation are not available in published reports and consist of fairly complex laboratory build and assembled gear.

The method described utilizes readily available commercial apparatus. X-rays of low intensity are passed through the patient's ventilating lungs, are detected by dual scintillation probes positioned over each lung, and after appropriate amplification are recorded on a dual channel Texas Recorder. The source of x-rays is an expensive portable machine operated at about 25 KV and less than 0.5 ma. The Dual Detection Scintillation System is available as a complete unit from *Picker* and consists of dual probes, rate meters and dual channel recorder. The total time required for the examination is 10-15 minutes and the irradiation received by the patient has been measured with a survey meter; it is less than 5 mr (milliroentgens).

Representative tracings obtained by this method in 100 patients with normal and diseased lungs will be presented. Exceedingly interesting findings have been obtained in various pulmonary diseases. Phase shifts of 180 degrees indicating completely paradoxic respiration in symmetric lung areas have been observed in lung tumors. Phase shifts and lesser degrees of phase lag, often illustrating a completely disorganized pattern, have been observed in emphysema, the abnormality of the tracing corresponding well with the severity of the process.

In contrast to bronchospirometry which has been used for many years to obtain information about individual lung function, this method yields its information without having to anesthetize the airway of the patient or placing large rubber catheters in his trachea and bronchus. The procedure is completely painless to the patient and does not subject him to any instrumentation. In addition this method permits study of a small portion of the lung whereas bronchospirometry estimates the function of each lung as a whole.

D 8. *Diagnosis of Shunts with Intracardiac Proportional-Counter Catheters—Preliminary Report.* **Marshall B. Kreidberg, Charles V. Robinson, and Harvey L. Chernoff (Department of Pediatric Cardiology, The Boston Floating Hospital; Physics Department, New England Center Hospital; and Departments of Pediatrics and Radiology, Tufts University School of Medicine; Boston)**

The purpose of this work is to develop a more accurate method for the diagnosis of left-to-right shunts in infants and children which does not require blood sampling.

Counter-catheters, each of which consists of a beta sensitive proportional counter of 2.1 mm diameter by 4 mm sensitive length connected to a plastic tube of the same diameter, are used to detect an inhaled or injected beta emitter. Placement of the intracardiac and intravascular counter-tipped catheters is done fluoroscopically in anesthetized dogs. Recordings of counts are made simultaneously from airway, aortic and right-heart counters to determine the appearance time of the beta emitter. Samples for subsequent assay are taken from the counter locations as a check against the recorded counts. Thoracic excursions, ECG and counts are recorded simultaneously. Normalcy of sacrificed animals is determined by autopsy. That of nonsacrificed normals is determined by pressure, oxygen and selective cinecardiographic studies. This plus knowledge of the surgical procedure verifies anomalies in the animals with created shunts.

Kr85 is administered either by injection (Kr85/saline) into the pulmonary artery or a vena cava or by inhalation.

Appearance times are determined by qualitative analysis of the recordings and are measured from the onset of inhalation or injection. Injections are made over a two second period, inhalations for 15 or 30 seconds.

The present phase of this study deals with the appearance times of the beta emitter in various intravascular and intracardiac locations. The average aortic appearance time is 2-5 seconds (mean 4 seconds) with inhalation, with injection 3-5 seconds (mean 4 seconds). Venous appearances were 15 seconds or later.

The second phase of this study is a repetition of the first in animals with created shunts.

Preliminary results obtained in intracardiac and intravascular beta detection with a proportional counter-tipped catheter are presented. Studies with this instrument in animals with shunts is underway. Clinically the use of a single right-sides counter-catheter with or without external in-vivo arterial counting is planned.

E 1. *The Association of Thyroid Cancer and Prior Radiation in Infancy and Childhood.* **Raymond G. Rose, J. H. Hartfield, and Eleanor MacDonald (Departments of Medicine and Epidemiology, M. D. Anderson Hospital and Tumor Institute, Houston)**

A review of this institution's series of patients with thyroid cancer is under way to determine whether antecedent X-irradiation had been given to the head, neck, or upper chest areas. A preliminary study indicated that 32 out of 63 patients interrogated had received such X-ray therapy in infancy or childhood. Currently complete information is available on 175 patients. Forty-six patients (26.3 per cent) gave a positive history of previous irradiation; in 34 cases, the irradiation was given before the age of 20. Thirty-eight of the patients were under 40 years of age when the diagnosis of thyroid cancer was established. The most common reason for X-ray therapy was management of acne. Data on X-ray dosage was obtainable in only a small number in cases: dosage ranged widely from 225 to 6300 r. A matched control group of 175 patients from the Strong Clinic had an incidence of 10 patients with a history of previous irradiation; of this number, however, only two had irradiation to the head, neck or chest region. The difference in the two series is significant at the 0.001 per cent level.

E 2. *Radioactive Yttrium (Y-90) in Interstitial Therapy.* **Joseph Greenberg and H. C. Dudley (Department of Nuclear Medicine, New York Polyclinic Medical School and Hospital, New York)**

Y-90, a 2.8 Mev pure beta emitter with a half life of 61 hours forms insoluble complexes with nucleic acids and has essentially ideal properties for use in local tissue destruction. It can be infiltrated as a solution or implanted into tissue as a soluble plastic filament which is fabricated by extruding from a heated die a mixture of methyl cellulose, propylene-glycol and radioactive yttrium. The radiation effect on the tissue concerned is sharply localized and predictable. There is complete cellular destruction within the mass containing the Y-90, with the zone of transition to normal tissue being approximately 50 microns. No significant translocation of the yttrium occurs and tissue repair at the radiation site is always complete. By adjusting the Y-90 content it is possible to ablate a small volume of tissue, or with high concentrations and multiple implants, to destroy any desired volume.

The lesions treated included 6 cases of advanced cancer of the bladder, 8 cases of prostatic neoplasm with urinary obstruction, 5 cases of recurrent retroperitoneal tumors which had become essentially radioresistant, 2 cases of epidermoid carcinoma of the tongue and 4 basal cell skin cancers. There were no significant deleterious effects and marked resolution of the tumor was achieved, with good relief of the local symptoms. A wide variety of obstructing luminal tumors of the coryna, bronchial tree, rectum etc. have been treated and good palliation obtained. The modality has been used successfully in relieving symptoms of benign prostatic hypertrophy causing severe urinary obstruction in 4 poor risk elderly patients, and in the elimination of resistant keloids and verrucae vulgaris in 4 patients. Y-90, applied topically in a blotter or bag, has also been found of value in the management of advanced surface malignancy such as necrotic skin metastases or bladder and vaginal or cervical erosion, with bleeding and/or infection.

E 3. *The Use of Intravenous P^{32}-labeled Colloidal Chromic Phosphate for the Prevention of Liver Metastases in Rats.* **Norman B. Ackerman, Arthur S. McFee, and Merle K. Loken (Departments of Surgery and Radiology, University of Minnesota Medical School, Minneapolis)**

Chemotherapeutic drugs have been shown, experimentally, to cause a decrease in the incidence of liver tumors produced by the injection of cancer cells into the portal veins of rats. It is felt that "unrooted" tumor cells are more susceptible to the effects of radiomimetic

agents than those cells already established in the "soil." Unfortunately, these agents are highly toxic, particularly to the bone marrow, and must be used with extreme caution.

In order to accomplish a similar decrease in incidence of liver "metastases" while avoiding bone marrow depression, a therapeutic dose of P^{32}-labeled colloidal chromic phosphate has been administered intravenously to rats. Approximately 85 to 95% of this material remains in the liver and most of the rest goes to the spleen. Only a negligible amount is taken up by the bone marrow.

The chromic phosphate (75 microcuries) has been given at the following time intervals before and after injection of 100,000 cells of Novikoff hepatoma into the portal vein: 24 hours before, 1 minute, 60 minutes and 24 hours after. Control animals, receiving tumor cells but no chromic phosphate have had a tumor incidence in the liver of approximately 70% Animals receiving P^{32}-labelled chromic phosphate one minute after the injection of hepatoma cells had a tumor incidence of 20 to 25%, representing a significant decrease in liver "metastases". The animals that were given chromic phosphate at greater intervals following tumor injection had smaller decreases in incidence of tumor "take" in the liver.

E 4. *Irradiation with Interstitial Radioactive Palladium.* I. Ariel and J. S. Robertson (Pack Medical Group, New York City and Medical Research Center, Brookhaven National Laboratory, Upton, Long Island)

Although irradiation of tumors by interstitial injection of Gold-197 and other isotopes has been established, there remains the possibility that other combinations of energy and dose rate may be even more effective. Among the likely contenders is palladium, which when activated by thermal neutron bombardment in a reactor yields principally two isotopes, Pd^{108} with a 17-day half-life and Pd^{109} with a 13.5-hour half-life. Appropriate combinations of activation times and decay times can give any desired ratio in the mixture of these two activities. This provides an unusual opportunity for comparison of the effects of various dose rates and durations of exposure.

After establishment of the feasibility and safety of the procedure, by injection of suspensions of colloidal radio-palladium and by insertion of radioactive palladium wires in muscles, liver and lung in rabbits, three patients with accessible tumors have been treated. Extension of the procedure to deeper tumors in combination with surgery is contemplated. Details of the histological and clinical findings will be presented.

E 5. *Changes in Hepatic Function Following Hepatic Irradiation by Y^{90} Microspheres.* Thomas Guzman, Merle K. Loken, Harlan Root, and John S. Perry, Jr. (Departments of Surgery and Radiology, University of Minnesota Hospitals, Minneapolis)

The effect of Beta irradiation of the liver utilizing radioactive ceramic microspheres as sources has been studied in dogs. Bromsulphalein retention, alkaline phosphatase, serum bilirubin, thymal turbidity and serum glutamic pyruvic transaminase (SGPT) were measured in animals before and at intervals following introduction of ceramic microspheres containing Yttrium-90 into the hepatic artery. Irradiation doses varying from 100 to 4000 rads/100 grams of tissue were delivered. None of the tests showed any abnormality except SGPT. These values rose sharply after the introduction of the radioactive sources and the increase was roughly proportional to the dose of irradiation administered. By the end of the sixth week, in most dogs SGPT values had fallen sharply but were still indicative of cellular changes in the hepatic parenchyma. Animals showed no physical signs of deleterious effects. Introduction of quantities up to 200 mgm of isotope free microspheres into the livers of control animals caused only minimal and transient elevation of SGPT values in a few animals and no significant change in other tests of liver function. The technique offers a possible method of irradiation of malignant tumors of the liver but requires more investigation.

E 6. *Organ Irradiation by Means of Radiating Microspheres.* **IRVING M. ARIEL (Division of Radioactive Isotopes, Hospital for Joint Disease and Pack Medical Group, New York)**

The availability of ceramic microspheres (3M) which are completely inert chemically and biologically and into which can be incorporated large numbers of radioactive isotopes, offers a new horizon for treating certain inoperable cancer. The microspheres measuring 60 microns in diameter, when injected intravenously will be over 99 per cent trapped within the pulmonic tissues. This offers an excellent means of giving irradiation to numerous metastases within the lungs. When administered into the hepatic artery they are almost completely retained within the liver, offering excellent means of irradiating hepatic neoplasms. When injected into the brachial artery or the femoral artery, they are completely localized within the extremity, none escaping into the systemic circulation. The entire extremity is thereby irradiated. This ability of irradiating microspheres to be completely trapped within a given organ or anatomic region offers an excellent means of giving large doses of irradiation to these organs harboring neoplasms. Thus, for pulmonary administration, from 100 to 200 millicuries of radioactive microspheres have been administered. In the irradiation of liver masses, 200 millicuries of microspheres have been given, and for extremities 50 to 80 millicuries of irradiating microspheres have been administered intra-arterially. The isotope which has been used in all instances has been Yttrium-90, this has an ideal radiologic spectrum. Distribution and histologic alterations following the administration of irradiating microspheres will be discussed. In several instances scandium-46 and chromium-51 also incorporated into irradiating microspheres have been administered for purposes of scanning. Scans made after the administration of isotopes will be presented.

Thirty patients treated to date with irradiating microspheres appear encouraging. Pain is relieved, tumors have shrunk and a sense of well being has been established. The complications within the dose range stressed above are minimal. With the exception of slight hypopyraxia and mild nausea and weakness which lasts from one to three days, there has been no marked complications. A new technique for administering intravenously and intra-arterially microspheres will be discussed (developed by Dr. John Kim of Ancker Hospital, St. Paul, Minnesota). Before the advent of this technique, the administration of the microspheres into arteries and veins by means of syringe injection have resulted in retention of the microspheres in some of the veins with a marked radiation reaction occurring. Alteration of the blood, liver function test and pulmonic function test have a minimum. These shall be discussed in detail.

Irradiating microspheres containing Yttrium-90 offers a new method of introducing into organs via the arterial system large doses of irradiation.

E 7. *The Simultaneous Intraperitoneal Administration of Nitrogen Mustard and Colloidal Radioactive P^{32} in the Rat: Gross and Histopathological Findings.* **LEONARD M. LIEGNER and NORMAN J. MICHAUD (Radiation Therapy Section, Department of Radiology, St. Luke's Hospital, New York)**

Rapid reaccumulation of malignant effusions that may occur soon after thoracentesis or paracentesis and subsequent to the instillation of radioactive colloids, such as $Au.^{198}$ or P^{32}, forces the Isotopist to prematurely drain fluids of high radioactivity. By so doing the full therapeutic effect of the isotope can not be realized.

On the other hand Nitrogen Mustard* administered similarly is believed to produce rapid changes in the body cavity surfaces, through its immediate chemical reactivity, without the problem of radioactive waste disposal or ineffectual drug administration resulting from its untimely withdrawal.

The use of radioactive isotopes continues as a preferred method of controlling malignant pleural effusion and malignant acites.

*Polyfunctional Alkylating Agent

$$CH_3-N < \begin{matrix} CH_2-CH_2-CL \\ CH_2-CH_2-CL \end{matrix}$$

Methylbis (βChloroethyl) amine.

Although the efficacy of Nitrogen Mustard for this purpose is in many instances comparable to the use of radioactive colloids, many occasions present themselves wherein an initial dose of Alkylating Agent fails to control the effusion whereas the radioisotope subsequently administered effectively does so.

It was reasoned therefore that the simultaneous administration of an immediate acting chemotherapeutic agent (Nitrogen Mustard) together with the more slowly acting, longer half-lived radioisotope (Colloidal Chromic-P^{32}) would appreciate synergistic effects; namely the rapid reduction in the reaccumulation rate of the malignant effusion thereby delaying the withdrawal of cavity fluid until the maximal radiation effect on the serous surfaces can be delivered by the decaying isotope. The dirth of literature reference and our own lack of knowledge as to the possible additive effects of such combined therapy both locally and systemically prompted animal studies on our part before embarking on therapy in patients.

Adult rats averaging 250 grams in weight were distributed among three experimental groups and a control group.

Group 1. Controls
2. Nitrogen Mustard alone
3. P^{32} (Colloidal) alone
4. Nitrogen Mustard simultaneously with P^{32} (colloidal)

Animals were individually housed and observations recorded on their behavior, general activity, appearances, gastrointestinal symptoms and survival.

Animals in each group were sacrificed at three days, one week, two weeks, three weeks and four weeks. Gross findings in the peritoneal cavity were noted and tissue specimen were taken of the porietal peritoneum, mesentery and small intestine. Each tissue specimen was fixed in cold acetone, washed, refrigerated for 24 hours following which they were placed in cedar wood oil for another 24 hours, cleaned in parafin in vacuum at 50°c. The specimens were then cut a 6 micron thicknesses, dried at 37°c. in an incubator and stained for the following:

1. Hematoxylin and Eosin
2. Glycogen (McManus Stain) (PAS) with control
3. Esterase and Napthol (Gomori Method)

The four groups of animals have been compared for general systemic effects, gross autopsy findings and histopathological changes.

A most significant occurrence was the marked intolerance of Group IV animals to the simultaneous instillation of Nitrogen Mustard and Colloidal P^{32}. Repeat studies within this group confirmed the lethality of the combination irrespective of whether 10 minutes or 24 hours was permitted to elapse between the administration of Nitrogen Mustard and the subsequently instilled colloidal P^{32}.

Reasons for the lethality of the combination are discussed. Experiments are in progress to clarify the mechanisms.

E 8. *Intravenous Colloidal Zirconyl Phosphate-P-32, Clinical Studies in Over 250 Cases.* J. M. Hill, E. Loeb and R. J. Speer (Wadley Research Institute and Blood Bank, Dallas)

Intravenous colloidal radioisotopes have been used in this clinic now for about ten years. This report is concerned with the preparation, distribution and dosage evaluation of colloidal zirconyl phosphate P-32. This particular colloidal radioisotope preparation has seemed to us to meet the needs for a stable, dispersed, radioactive colloid suitable for intravenous or intracavitry use with a suitable type of beta irradiation and features of convenience and economy having to do with ease of preparation.

The clinical experience during the ten year period with median survival calculation from onset of disease, diagnosis, and treatment in chronic leukemia and lymphomas is presented.

The simple preparative technique has been described. The product by electron microscope has shown a colloid micelle of less than 0.05 micron in diameter. The preparation is sterile, non-pyrogenic and has an exceptionally low percentage of dialyzable radioactivity, routinely held to less than 2% of the total activity. The colloid has proved to be very stable and can be stored at 4° C. for several weeks without formation of visible sediment.

Following intravenous injection, colloid distribution in general appears to follow the distribution of reticuloendothelial tissue of the various organs and of their associated phagocytic activity, thus providing an agent for the rather selective irradiation of these areas. Other tissues of the body appear to receive insignificant amounts of irradiation during such therapy.

This clinical experience seems important from two points of view: first, the study of any side effects, i.e., acute or accumulative chronic effects of any part of the colloidal nicelle whether zirconyl ion or the compound as a whole; and, second, the record of therapeutic effectiveness as indicated by the median survival time of the patients in the different categories.

Case reports illustrate the use of this product and other combinations of treatment.

Our philosophy of treatment is discussed and results evaluated. Our goal has been prolonged remissions, with long intervals of treatment-free episodes, and we feel that this has been achieved with colloidal radioisotopes and further that undesirable toxic effects or other peculiar side effects have not been observed due to the zirconyl ion either at short range or over a long period of time.

E 9. *Selective Tumor Response to Neutron Capture Therapy of Transplantable Neoplasms in the Mouse.* **Lee E. Farr and T. Konikowski (Medical Department, Brookhaven National Laboratory, Upton, Long Island)**

Utilizing the interaction of thermal neutrons and boron 10 to liberate in situ alpha particles and energetic lithium atoms, studies have been carried out of tissue and neoplasm responses in relation to boron content. While the mechanism of the reaction logically would seem to depend upon liberation of energetic heavy particles, comparison of responses of vascular and neoplastic elements, when implanted into muscle, with muscle and skin structures does not clearly support this hypotheses as the sole factor. A transplantable sarcoma of mice capable of causing death in four weeks was used in inbred Swiss mice. The Brookhaven Medical Research Reactor provided thermal neutrons. Boron was given as sodium pentaborate in aqueous solution, intravenously, in doses equivalent to 35 milligrams of boron per kilogram observed body weight. Exposure to thermal neutrons was provided twenty-five to thirty minutes later.

The effects upon neoplasms were followed by measurement of size and by histological preparations. Only final effects were noted in skin, muscle and its component vascular structures. Boron concentrations in blood, neoplasm and muscle were measured by a method as yet unpublished but in our hands proving to be the most reliable estimation available. Data will be presented showing gross and histologic alterations as a result of the manipulation and a non-responsiveness of hair follicle structures and skin under certain conditions but under others a destructiveness similar to but less than that observed in neoplasms. Absolute control of neoplastic growth could be achieved. Some dosimetric implications of these observations will be discussed.

E 10. *The Comparative Lethal Radiation Dose of P-32 when Administered as Mono-Phosphate and Polymetaphosphate.* **Roger Veatch and Ervin Kaplan (Radioisotope Research Section, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)**

The evaluation of therapeutic effectiveness of P-32 labeled polymetaphosphate in treatment of carcinoma of the prostate metastatic to bone, has indicated the need for determination

of the comparative minimum lethal dose (MLD^{50}) from radiation effect when P-32 is administered as polymetaphosphate as compared to monophosphate.

The MLD^{50} was determined on Swiss-Webster male albino mice of 20-25 gram weight. The P-32 activity was injected via the intraperitoneal route. The dosage of P-32 activity was 2, 4, 6, 8 and 10 uc per gram of mouse. Ten mice were injected for each dose indicated above for both polymetaphosphate and monophosphate studies. The amount of carrier phosphate or polymetaphosphate was independent of radioactivity dosage and was constant per gram of mouse.

The results of the above study indicated an MLD^{50} in 30 days of 4.5 uc per gram for monophosphate and no significant lethal effect up to 10 uc per gram for polymetaphosphate. The dosage necessary to produce an MLD^{50} for this substance is currently being evaluated.

The difference in lethal effect may be related to altered distribution within the organism, which has previously been demonstrated or may be secondary to a decrease in effective biological half-life which is also under study. Should the decrease in lethal effect with polymetaphosphate be attributable to distribution, the margin of safety in therapy would be enhanced for this preparation.

E 11. ***Hematologic and Tumor Response to Low Dose Uniform Total Body Irradiation.*** **Melville L. Jacobs (Department of Radiology, City of Hope Medical Center, Duarte, California)**

A specially designed concrete-walled chamber houses eight sources of cesium^{137} of 300 curies each. The chamber is so designed that almost completely uniform total body irradiation can be achieved. The dosimetry is briefly reviewed.

A group of patients suffering from acute leukemia and another group with disseminated malignant neoplasms have been treated with low dose total body irradiation. The hematologic and tumor response is presented. In addition, a small group of patients suffering from disseminated malignant neoplasms is being treated with larger doses of total body irradiation and their response will be compared with those in the lower dose range.

The hematologic response is different in leukemia from that in disseminated neoplasms. In the latter, the drop in the white count occurs far more slowly. A striking tumor response to 300 rads was noted in one patient out of seven treated with Total Body Irradiation.

F 1. ***Statistical Analysis of Eight Years Experience in Positron Scanning for Brain Tumor Localization.*** **Saul Aronow, Gordon L. Brownell, Sara L. Lovo, and William H. Sweet (Massachusetts General Hospital, Boston)**

Over the past nine years positron scanning for brain tumor localization has become a routine diagnostic procedure at the Massachusetts General Hospital. The apparatus used coincidences of the annihilation radiation from positron emission to obtain good collimation with high sensitivity.[1] The output picture is a direct mechanical print. The most frequently used tracer is As^{74} in the form of sodium arsenate. Chemical agents using other positron emitters are described.[2] The design of the apparatus and the technique stress simplicity and reliability with a minimum of training on the part of the operating personnel.

The scanner produces two pictures simultaneously. One is a parasagittal projection with high definition; the other indicating any lateral unbalance. If desired, an A-P view may be obtained by turning the patient's head.

The histories of the patients scanned have been extracted, and a coding scheme devised to record the data on IBM cards. This has allowed the use of an electronic computer to analyze the results of scanning in a detailed manner.

The results of this analysis on the 4500 patient scans is presented. The scan classification, "Abnormal," "Probably Abnormal," "Probably Normal" or "Normal," is compared to pathology or other definitive diagnoses, broken down by type of disease. For glioblastoma multiforme and meningioma, over 90% are correctly indicated as abnormal. Other tumors are less positive.

Vascular problems indicate abnormality in varying degree dependent on the specific disease. Nonorganic diseases show from 5 to 15% false positives.

Scanning results are also compared with other neurosurgical diagnostic procedures as a function of specific disease. The comparison indicates that positron scanning is a valuable aid to neurosurgical diagnosis.

F 2. ***Body-Section Radioisotope Scanning.*** **DAVID E. KUHL and ROY Q. EDWARDS (Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia)**

With scanning methods now employed, images from all levels in the body are superimposed on the recording. As a consequence of this overlapping, the image of a tumor may be lost in a confusion of patterns resulting from overlying or underlying radioactivity. This restriction can be avoided by application of tomographic methods which differentiate the image sections one from the other. Only those images of radioactive structures located in a specific section of the body are clearly demonstrated on the recording, while the unwanted images of structures above or below are eliminated.

A clinical scanning system is presented which will provide depth discrimination of radioactivity images in the liver, brain, thyroid gland, and other organs.

F 3. ***Demonstration of Myocardial Infarcts by Photoscanning.*** **EDWARD A. CARR, JR., WILLIAM H. BEIERWALTES, AUDREY V. WEGST and JOHN D. BARTLETT, JR. (Departments of Internal Medicine, Pharmacology and Radiology, Clinical Radioisotope Unit and Kresge Research Radioisotope Unit, University of Michigan, Ann Arbor)**

Scintillation scanning after administration of Mercury-203 labeled chlormerodrin (Neohydrin) has been used to diagnose lesions of brain and kidney. The present work reports visualization of myocardial infarcts by external scintillation scanning, using this compound.

In seven dogs the anterior descending branch of the left coronary artery was ligated and the incision closed. Four sham-operated dogs were controls. Each dog received 700 μc of Hg^{203}-chlormerodrin intravenously 1 to 4 days post-operatively. Photoscanning of the thoracic area of the anesthetized dogs in supine position was performed, using a 3″ x 2″ crystal ("Magnascanner") and 19-hole collimator. Scans 1½ to 25 hours after isotope administration showed localized "hot" areas clearly suggesting infarcts in the ligated living dogs' beating hearts. By transfixing each heart with needles after scanning and removing the anterior chest wall with the dog still in scanning position, each heart was exposed and its outlines projected on the scan. The "hot" areas corresponded to infarcted or ischemic areas. Re-scanning of excised hearts, emptied of blood, confirmed the "hot" areas. Controls were negative. Samples from normal and abnormal areas of heart and other tissues were counted in a well-type scintillation counter. All left ventricular samples were examined histologically. Mean Hg^{203} concentrations (cpm/gm) in infarcts and non-infarcted ischemic areas were 630% (range, 270% to 1270%) and 350% (220% to 580%), respectively, of that in normal left ventricular tissue, and 480% (130% to 1240%) and 350% (85% to 1140%), respectively, of that in blood. Hg^{203} concentration among multiple samples from controls showed little variation within a given left ventricle.

Hg^{203}-chlormerodrin thus allowed demonstration of myocardial infarcts in vivo by external photoscanning and this was confirmed by re-scanning excised hearts and by tissue counting.

The in vivo studies are being extended to man.

F 4. ***The Interpretation of Renal Photoscans.*** **RAYMOND S. KIBLER, MONTE BLAU, and MERRILL A. BENDER (Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo)**

In this laboratory, the radioisotopically tagged mercurial diuretic, Hg-203 Neohydrin, has proven to be an effective agent for renal photoscanning.

At the present time, an intravenous dose of 150 microcuries of Hg-203 Neohydrin is employed and scanning is started within 1-2 hours after administration. The techniques and equipment employed, including a closed-circuit television system, have been reported in earlier communications.

While we are accumulating experience in defining the normal range of variation, we are investigating a variety of renal disorders with special emphasis on space-occupying lesions—correlating the scans with surgical and/or pathological findings.

The evaluation of these scans includes the systematic estimation of: a) size, shape, outline and position of both kidneys, b) the relative concentration of the isotope on both sides, c) any displacement and/or rotation, d) alteration in size and configuration of the interrenal space, and e) the outline of the spleen and liver.

Our studies would indicate that renal photoscanning with Hg-203 Neohydrin not only help to confirm but also amplify upon the information obtained by the more conventional techniques of intravenous and retrograde pyelography and aortography. Infrequently the method may demonstrate the presence of space-occupying lesions which are not detectable by these other procedures.

F 5. *Renal Scanning.* Prentiss M. Dettman, and R. T. Brooks (Radioisotope Laboratory, National Naval Medical Center, Bethesda)

Photoscans of the kidneys have been performed on 100 patients in an attempt to determine the value of this procedure. Hg^{203}-Neohydrin^{R} is the test agent. A dose of 50 microcuries for adult patients is most satisfactory. Doses of 100 microcuries or more may obscure some lesions. Renal uptake of the Hg^{203}-Neohydrin^{R} reaches a relative plateau in 30-45 minutes. Satisfactory scans are obtained one hour after administration. Scans at 24 hours do not contribute further information.

The scans very satisfactorily portray the size and shape of the functioning renal parenchyma. Mass lesions are easily demonstrated. Diminished localization of the Hg^{203}-Neohydrin^{R} appears to be a very sensitive measure of function. "Absent" kidneys have been found. Areas of vascular impairment and localized infection have been shown. The scan is especially valuable in patients who are sensitive to the radiopaque media for excretory pyelography.

Results to date show that renal scans are an excellent diagnostic supplement to the intravenous pyelogram and radioactive renogram. In many instances of localized lesions the scans are superior.

F 6. *Stop-flow Renal Scans.* J. L. Izenstark, J. U. Schlegel, and R. O'Dell (Departments of Radiology, Surgery, and Urology, Tulane University and Charity Hospital, New Orleans)

Currently performed scintiscans of the kidneys require either a constant infusion of radioactive material, or an agent which is "fixed" in the renal tubule. Moderately high doses of radiation are used, and there is a high background rate. The scan represents the functioning renal tissue and the calyceal-pelvis system. The radioactivity in the calycealpelvis system may occlude small areas of decreased or absent radioactivity in the renal tubules.

Utilizing the principle of urinary "stop-flow" (brief occlusion of the ureters during osmotic diuresis) improved scintiscans of the kidney can be obtained. Low doses of radioactive iodine are used and this is rapidly excreted when "stop-flow" is released. Furthermore, only the functioning renal tubules are represented on the scan. Examination of renal tissue from dogs during "stop-flow" has shown that radioactivity is concentrated in the renal cortex, and the renal medulla is virtually free of radiation.

Scintiscans performed on dogs and humans will be shown.

F 7. *Diagnosis of Splenic Disease by Radioisotope Scanning.* **HENRY N. WAGNER, JR. and JOHN G. MCAFEE (Diagnostic Radioisotope Laboratory, The Johns Hopkins Hospital and University, Baltimore)**

Distinctive patterns of sequestration of human, canine and rabbit erythrocytes were observed depending on the degree of damage to the red cells. Early signs of injury, produced by heart-treatment for 60 minutes at 50°C or by exposure to low doses of the sulfhydryl-inhibitor, N-ethyl maleimide, resulted primarily in splenic sequestration of the erythrocytes. More severe injury to the red cells, produced by more prolonged heating or by exposure to higher doses of NEM, resulted in both hepatic and splenic sequestration of the red cells. Very severe damage resulted in hepatic, rather than splenic sequestration.

Measurement of the splenic arteriovernous difference in concentration of heat treated Cr^{51} labeled red cells permitted calculation of the splenic extraction ratio and measurement of splenic blood flow in the dog.

Patients with congestive splenomegaly had an increased rate of clearance of damaged red cells from the circulation as a result of enhanced splenic sequestration. Patients with sickle cell disease had an impaired clearance of damaged red cells from the circulation.

The technique selected for splenic scanning as a diagnostic procedure was to heat red blood cells at 50°C for one hour, after labeling with 300 microcuries of Cr^{51} in A.C.D. solution. Scanning was performed one to 24 hours after intravenous injection of the heated cells.

Splenic scanning has proved of clinical value in the differential diagnosis of obscure masses in the left upper quadrant of the abdomen, in the diagnosis of splenomegaly not clinically detectable, in diagnosing space-occupying lesions of the spleen, in the quantitative assessment of splenomegaly, and in the detection of the absence of functioning splenic tissue.

F 8. *Localization of Antifibrin Antibodies in Human Tumors.* **W. C. DEWEY, W. F. BALE, R. G. ROSE, and D. MARRACK (Departments of Physics, Medicine, and Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston; and Department of Radiation Biology, University of Rochester School of Medicine and Dentistry, Rochester, New York)**

Day, Planinsek, and Pressman of Roswell Park Memorial Institute (*J. Nat. Cancer Inst. 22:*413, 1959) and Spar, Goodland, and Bale of the University of Rochester (*Proc. Soc. Exper. Biol. and Med. 100:*259, 1959) found that antibodies prepared in the rabbit against rat fibrin localized preferentially in the Murphy-Sturm lymphosarcoma in the rat. Using antibodies heavily labeled with I-131, Bale, Spar, and Goodland (*Cancer Research 20:*1488, 1960) have been successful with radiation therapy in rats bearing these tumors. They have extended their studies to dogs and have found excellent localization in some tumors with the best results in sarcoma (*Cancer Research 20:*1501, 1960). They also found that the administration of epsilon amino caproic acid (EACA), which inhibits the fibrinolytic system, greatly increases the apparent uptake of the antibody by some tumors. This localization phenomenon is probably associated with the deposition of fibrin.

Through collaboration between the University of Rochester and M. D. Anderson Hospital, these studies have been extended to humans. Results indicate that antibodies prepared in rabbits against human fibrin may localize in malignant tissue, especially melanomas and sarcomas, at a concentration 20 times or more than found in normal tissues. No preferential localization is found in any normal tissue, and the biological halflife is about 5 to 8 days. The maximum uptake by the tumor is achieved at 3 to 6 days after injection, and with the use of EACA the ratio of antibody concentration in the tumor to that in normal tissues continues to increase for several days. Possibilities for diagnosis and therapy will be discussed.

F 9. *The Clinical Use of the Autofluoroscope.* **MERRILL A. BENDER and MONTE BLAU (Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo)**

The autofluoroscope is a non-scanning device designed to give a graphic representation of the distribution of gamma emitting isotopes within the human body. The instrument incorporates the important features of modern scanners including collimation with a good depth response and adequate resolution, high efficiency and a high contrast data presentation system.

The detector consists of 293 two-inch thick, three-eights inch diameter NaI (T1) crystals hex packed in a 6 x 9 inch array. The collimator provides a single tapered aperture for each crystal, 12 three-inch multiplier phototubes separated from the crystal bank by a four-inch thick lucite light pipe. A photopeak interaction occurring in any crystal is represented as a dot of light in the corresponding location on the face of an oscilloscope by a modification of the data transfer system devised by Anger.

The first advantage of the autofluoroscope over radioiostope scanners is a marked reduction in the time required to make an examination. Using the same dosage schedule brain and liver tumors are localized in one-tenth the time needed for conventional scanning.

The second advantage is related to the fact that information is collected from an entire organ at the same time. This permits the visualization of dynamic processes and the use of isotopes or labelled compounds having exceedingly short physical or biological half-lives. With decreasing half-life, there can be a commensurate increase in administered dose resulting in even shorter examination times. Exposure times can be so short that cinephotographic techniques are now used for the visualization of the passage of I-131 labelled Hippuran through the kidneys and for circulation studies with Ba-137m the 2.6 minute half-life daughter of Cs-137.

F 10. *Clinical Experience with Se^{75}-Selenomethionine for Pancreas Visualization.* **MONTE BLAU, ROBERT F. MANSKE and MERRILL A. BENDER (Roswell Park Memorial Institute, Buffalo)**

Animal experiments (J. Nuclear Med. 2:102, 1961) have demonstrated the feasibility of pancreas visualization by scanning techniques using gamma emitting amino acid analogs. This report deals with the use of Se^{75}-selenomethionine in humans.

The pancreas specificity of amino acids is based on the rapid synthesis of the digestive enzymes. The pancreas tissue itself is not labeled but the radioisotope is taken up by the enzymes in process of synthesis. The following protocol has been evolved to provide the maximum stimulation of uptake without risk of rapid secretion of the labeled protein. Four or more hours after the last meal (usually breakfast) a dose of mixed intestinal hormones (Cecekin Vitrum) is given to empty the pancreas. One hour later 3 microcuries/kilo of Se^{75}-selenomethionine is administered I.V. Scanning is started in one-half hour and can be repeated for up to 2 or 3 hours. This procedure has been generally satisfactory but it has not produced uniformly good scans in all patients and other protocols are being investigated.

The biological half-life of Se^{75}-selenomethionine in rats and mice is 15-20 days. If this data is valid in humans the total body dose from a scanning dose is about 600 mrad delivered over several months. The pancreas concentration is transient and there is no important local radiation there or elsewhere.

Biochemical studies in humans on rates of blood protein synthesis, intestinal absorption, etc. have been carried out using Se^{75}-selenomethionine as a conveniently measured gamma emitting amino acid.

F 11. *Liver Function As Related to Thyroxine Metabolism.* **L. VAN MIDDLESWORTH, JO AUDREY TURNER, and ALYS LIPSCOMB (Divisions of Physiology and Medicine, University of Tennessee, Memphis)**

In 1949 when I-131 thyroxine became available, Keating and Albert (J. Clin. Endo. 9:1406, 1949) showed that 10% of an oral dose of DL-thyroxine was accumulated by the human liver in 6 hours. We have studied I-131 L-thyroxine metabolism using photoscanning technique. In 3 patients with no evidence of liver disease, 6 hours after an oral dose of 60 microcuries of I-131 L-thyroxine, the liver was clearly and intensely outlined by the photoscan technique. After 24-48 hours the liver, and to a lesser extent, the transverse colon were clearly silhouetted on the photoscan. After 48-96 hours only the liver outline was shown. In 3 patients with Laennec's cirrhosis, the liver was very difficult to detect and the only area of sharp contrast was the colon. Thus, the intensity of the photoscan of liver exceeded colon in the normal cases while the scan of the colon was much more intense in cirrhosis.

This technique may be helpful in the following: (1) study of the metabolism of thyroxine, (2) study of the intestinal tract by the introduction of a negligible quantity of contrast medium, (3) as a physiologic liver function test. For liver studies this method has the unique advantage of utilizing tracer quantities of a normal metabolite, thyroxine, labeled with radioiodine.

G 1. *Distribution, Excretion and Metabolism of C-14 Etryptamine Acetate in Man.* **JOHN H. NODINE, JOSEPH M. PLATT, and ARNOLD DUCANES (Section of Clinical Pharmacology, Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia)**

Six depressed patients over 40 years of age were given 20 μc of C-14 etryptamine acetate (Monase) along with 30 mg. of stable drug. Serum, urine, and feces were collected for 48 to 72 hours for determination of acute kinetics: a) gastrointestinal absorption rate, b) serum disappearance rates, c) dilution spaces, d) renal clearance rates and e) rate of conversion to metabolites. All samples were determined in duplicate and appropriate constants with their confidence limits determined from the regression analysis of the data. The same study was repeated after two weeks of loading with stable etryptamine acetate (90 mg. daily).

The half time of gastrointestinal absorption was about one-half hour. Serum radioactivity reached a peak at two hours and disappeared according to a monophasic straight line semilogarithmic regression. The calculated dilution space exceeded the total body water, suggesting intracellular concentration of etryptamine, since G.I. absorption was nearly complete as shown by the cumulative urinary excretion curves. Renal serum clearance averaged three to four liters per hour. Because of the large "dilution" space, this clearance rate corresponded to removal from the space with a half time of ten to fifteen hours.

Further chromatographic studies are in progress to identify and quantitate the conjugate and metabolites of etryptamine and to compare these before and after drug loading.

G 2. *Fate of Alykylated 6-S^{35}-Mercaptopurine in the Rat.* **HANS J. HANSEN, GARY GILES, and SAMUEL B. NADLER (Department of Biochemical Research, Touro Infirmary and the Departments of Medicine and Biochemistry, Tulane School of Medicine, New Orleans)**

The mechanism of action of 6-MP in the inhibition of human leukemia and certain animal neoplasia is at present unknown. One of the current theories includes the hypothesis that the ribotide of 6-MP constitutes the lethal compound effective in the control of neoplastic cellular growth. The data indicate that alkylated derivatives of 6-MP may be as effective as unsubstituted 6-MP. Since alkylation occurs in the 9 position, at which point ribotidization must occur, it was of some interest to determine whether or not the intact organism can de-alkylate these compounds in order to allow for ribotide formation.

The sulphur-35 derivatives of 6-MP, 9-methyl - 6-MP, and 9-ethyl - 6-MP were synthesized in relatively pure form and administered to rats in pharmacological doses of 4 milligrams per kilogram. The urinary excretion of the metabolites was studied. Unsubstituted 6-MP was found to be excreted in rat urine as thiouric acid chiefly. The alkylated derivatives, however, were found excreted in their original form. If de-alkylation of these derivatives had occurred to any appreciable extent, one could reasonably expect the appearance of thiouric acid in the urine. The data indicate that de-alkylation does not occur at the 9 position. It is inferred that ribotide formation cannot take place unless the unsubstituted 9 position of the purine ring is available for this process. It is concluded that the activity of 6-MP may be accounted for on some other basis than on the formation of a lethal ribotide.

G 3. ***Radioactive Modified Insulin: Method of Preparation and Comparison with Radioactive Crystalline Insulin in Human Subjects.*** **LEONARD R. ROBBINS, DAVID DWIGHT ODOM, PHILIP C. JOHNSON and HAROLD L. DOBSON Department of Medicine, Metabolic Section, Baylor University, College of Medicine, Houston)**

The metabolism of crystalline Insulin-I-131 has been widely explored. Although more important therapeutically, Insulin modified by additional protein has not been so studied. We have undertaken such a study in human subjects and wish to report our methods. A modified insulin-I-131 was prepared in the manner of NPH insulin utilizing protomine zinc insulin and Iodoinsulin-I-131 (Abbott). Paper chromatographic studies have demonstrated the similarity of the prepared insulin to commercial NPH insulin. One unit (approximtaely 150,000 CPM) was diluted with saline to 0.5 ml, mixed, and injected. One minute counts were made with a scintillation counter every 10 minutes until the counting rate had decreased to one-half. Comparison observations were made utilizing different injection sites and crystalline insulin-I-131— in the same subjects. Normal controls, diabetic patients not previously treated with insulin, diabetic patients long under therapy with insulin, and diabetic patients with special problems of insulin allergy and insulin resistance were studied. Our results with radioactive crystalline insulin are (half-time of absorption).

Normal controls	137.6 ± 5.9 minutes
Diabetics on diet only	145 ± 16.5 minutes
Diabetics on oral agents only	183.4 ± 16.1 minutes
Diabetics on oral agents (previously on insulin)	215.1 ± 23.7 minutes
Diabetics on oral agents and insulin	189.5 ± 17.0 minutes
Diabetics on insulin	187.9 ± 12.5 minutes
Diabetics with dematological reactions	191.8 ± 13.0 minutes

Our results with labeled modified insulin reveal similar differences with, interestingly, a faster absorption rate in patients on oral agents than in controls. Our results range from 197-578 minutes (half-time of absorption) with an average of 301 minutes.

The important implication from this work regarding the time of administration of insulin and its relationship to meals, etc. should improve our understanding of the practical problems in the management of diabetic patients with intermediate acting insulin.

G 4. ***Investigations of P-32 Tagged Triethylene-Thiophosphoramid In Isolation Perfusion Techniques.*** **D. B. ROCHLIN (Los Angeles)**

G 5. *A Double Isotope Derivative Method for the Assay of Progesterone.* **C. A. Woolever and Alan Goldfien (Department of Obstetrics and Gynecology, University of Colorado, Denver, and University of California Medical Center, San Francisco)**

Studies of the metabolism of progesterone have been hampered by the lack of a specific and sensitive method for the measurement of this steroid in plasma. Application of the double isotope derivative method offered a solution to this problem.

The usual derivatives that is used in methods of this type is a tritiated acetate. Since progesterone can not be acetylated, an alternative was devised by reducing the steroid with sodium borotritide followed by partial re-oxidation with manganese dioxide. The resultant product is isolated and purified by paper chromatography prior to counting.

The accuracy of the method was demonstrated by assay of solvent samples prepared to contain 1.06 ug, 0.53 ug, 0.265 ug, and 0.1 ug of progesterone. Results of this analysis were 1.06 ± 0.018, 0.52 ± 0.014, 0.25 ± 0.012, and 0.094 ± 0.007 respectively. Two pools of pregnancy plasma were analyzed, using 12 samples of each (5 ml and 10 ml per sample). The first was found to contain 0.12 ± 0.005 ug/ml, and the second 0.17 ± 0.01 ug/ml. Another study showed that as little as one milliliter of pregnancy plasma was sufficient to give an accurate result.

Authentic progesterone was added to male plasma in amounts of 0.1 ug and 0.2 ug per 5 cc of plasma for recovery studies. The measured values of 0.140 ± 0.008 ug/5ml and 0.232 ± 0.04 ug/5ml, when compared to values of 0.033 ± 0.009 ug/5ml, led us to believe that the latter value represents progesterone endogenous to male plasma.

The specificity of the method is shown by a comparison of partition coefficients. Derivatives were made from authentic progesterone-4-C^{14} and from a plasma extract. Aliquots of each were partitioned in two systems. The resultant coefficients were 2.86 vs. 2.87 and 0.225 vs 0.219.

A similar technique for measurement of plasma estrogens is being developed.

G 6. *Studies on the Antigenicity of Insulin with I^{131}-labeled Insulin.* **Rosalyn S. Yalow and Solomon A. Berson (Radioisotope Service, Veterans Administration Hospital, Bronx)**

Studies with insulin-I^{131} have demonstrated the ubiquitous presence of antibody in the plasma of patients treated with commercial mixtures of beef-pork insulin for longer than 6 weeks to 3 months. The amino acid sequences of pork and human insulin differ only in a single terminal amino acid of the B chain while beef insulin differs from human insulin in addition at positions 8 and 10 of the A chain. It is of interest to clinical problems associated with insulin therapy as well as to immunochemistry to evaluate the relative antigenicity of beef and pork insulin in man and to study the reaction of beef, pork and other species insulins and their chemically modified derivatives with human antibody to known species insulin. Antiserums for these studies are obtained from patients treated with only beef, only pork or mixtures of beef-pork insulins. The direct reaction of I^{131}-insulin of various species with antibody and the competitive inhibition offered to this binding by the presence of unlabeled insulin of the same and different species insulins are studied using previously described techniques of paper chromatoelectrophoresis. Results obtained indicate that pork insulin as well as beef insulin is antigenic in man and that the antibody formed subsequent to pork insulin therapy reacts with insulin at positions other than the site of amino acid difference. Significance of these findings will be discussed.

G 7. *Metabolic Fate of* In Vivo *Labeled Rat Erythrocytes.* **Bergene Kawin and Jeng M. Hsu (Radioisotope Service and Biochemistry Research Laboratory, Fort Howard and Baltimore Divisions, Veterans Administration Hospital, Baltimore)**

Observation at an early date of pronounced splenic accumulation of Cr^{51} administered to rats has suggested possibilities of Cr^{51} incorporation into metabolic processes of this tissue. The present study measures Cr^{51} red cell survival time and tissue distribution in normal rats following *In Vivo* administration of the radioisotope.

Apparent erythrocyte survival time was in agreement with other studies, and graphical analysis of data showed that liver and kidney Cr^{51} "space" remained constant with no indication of accumulation, but in spleen net uptake of Cr^{51} labelled red cells increased with time. Splenic accumulation of Cr^{51} was delayed for a time period almost as great as the erythrocyte survival time itself. The kinetic rate and extent of splenic accumulation of Cr^{51} could not be directly accounted for by sequestration of labelled red cells alone.

Related studies utilizing C^{14} will be compared and mathematical relationships of these findings will be presented and discussed.

G 8. *Tritiated Thymidine as an Investigative Tool in the Study of Malignant Disease in Animals and Humans.* **Eugene P. Frenkel, Charles T. Knorpp and Donald R. Korst (Simpson Memorial Institute, University of Michigan, and Radioisotope Service, Veterans Administration Hospital, Ann Arbor)**

Employing a tracer type of assessment of the fate of the isotopically (tritiated or C-14) labeled nucleic acid precursor thymidine (Tdr), the progress of the dynamics of DNA synthesis in tissues can be followed. Evaluation of the pattern of precursor incorporation is made by means of autoradiographic tissue studies for information concerning the specific cell types which are active and their "synthesis or regeneration" time, and also by means of rapid liquid scintillation counting of a total hydrolyzed tissue extract.

Studies were carried out in normal rats and patterns of precursor incorporation were delineated in plasma, liver, spleen, thymus, bone marrow and dextran-separated WBC's. Following a cytotoxic (anti-neoplastic) agent there is a temporary interruption of tissue DNA synthesis, the degree and duration of which is dose dependent with a sequential return of synthesis in gut, marrow, thymus, spleen and then liver. During recovery, DNA synthesis reveals a periodicity of tritiated thymidine incorporation with individual tissue variation.

In humans, there is also a pattern of precursor incorporation with in vivo administration and serial assessment of dextran-separated WBC's and bone marrow. By contrast, in chronic granulocytic leukemia there is markedly delayed release and evidence of prolonged synthesis time of the neoplastic white cells. In acute leukemia, an intermediate time (between the normal and the prolonged time of chronic granulocytic leukemia) was seen.

Thus, this technique affords a dynamic assessment of DNA synthesis in neoplastic disease. Preliminary evidence reflects a prolonged interval of DNA synthesis and cell release in the leukemias.

G 9. *Glucose Kinetics and Oxidation and the Effects of Insulin, Tolbutamide and Phenethylbiguanide (DBI) in Normal Human Subjects.* **Myron Pollycove (Donner Laboratory, University of California, Berkeley)**

Simultaneous tracer studies by glucose kinetics and oxidation in "normal" subjects have been analyzed only by Baker, et al., in a study of 4 patients. Because of the paucity of available data, it seemed desirable to include in this investigation a relatively large group of normal individuals for repeated measurements. Since the modes of action and effects of insulin, tolbu-

tamide, and phenethylbiguanidine are to a large extent unknown and remain highly controversial, the effects of these compounds upon glucose kinetics and oxidation were also measured in the normal subjects of this study.

Blood sugar concentration, glucose specific activity and breath $C^{14}O_2$ specific activity were determined before and after intravenous injection of 10 to 14μc uniformly labeled C^{14} glucose in 46 complete studies of 10 normal male subjects ages 19 to 47, and one 48 year old obese but otherwise normal female subject. Mean values for the male subjects are: blood glucose 78 mg/100 ml; miscible glucose pool, 28g/Kg with a fractional turnover of 0.48/hr; 40% of the turnover is oxidized hourly (0.052 g/Kg/hr); 54% of the CO_2 pool (0.51 g/Kg) is expired hourly (0.27 g/Kg/hr) of which 28% is derived from glucose oxidation. Glucose oxidation in the obese subject corrected to average weight was markedly decreased to 0.015 g/Kg/hr, 29% of normal.

Insulin given intravenously (0.1 units /Kg) or subcutaneously (0.2 units/Kg) increased glucose oxidation and simultaneously inhibited andogenous release of insulin. Oral administration of 100 mg phenethylbiguanide (DBI) appeared ineffective.

G 10. *Estimation of Human Intestinal Function by Biochemical Biopsy and Uptake of Radioactive Nutrients.* Ted M. Bow and Richard P. Spencer (Department of Biophysics, University of Buffalo School of Medicine and Radioisotope Service, Veterans Administration Hospital, Buffalo)

Functional tests of intestinal activity are limited by the fact that the blood level at any point in time is given by $V.dB/dt = dE/dt - dU/dt$, where V represents the volume of distribution, B the blood concentration, t time, E entry and U utilization. Hence 2 unknowns are involved E and U), and exact solution for the rate of entry can often not be achieved. A new approach is to study the ability of intestinal tissue to take up nutrients in vitro. Human intestinal tissue was obtained at the time of operation, or by use of the Crosby-Kugler biopsy capsule. Tissue was incubated with approximately 10 times its own weight of pH 7.4 Krebs-bicarbonate buffer, containing the radioactive material under study adjusted to an appropriate concentration by addition of carrier. Human small intestinal segments accumulate amino acids under these conditions and their action on other nutrients is under investigation. Segments of intestinal tissue are used to produce a 5% homogenate, which is assayed for enzyme activity. Initial enzymes studied have been lactic dehydrogenase, glutamate-pyruvate transaminase and alcohol dehydrogenase. All can be demonstrated to be present, but in differing specific activity as one descends the small gut. Hence a gradient may exist in the human small gut, of enzyme activities, as it does in the intestine of laboratory animals. The study of segments of human small intestine by use of the uptake of radioactive nutrients and estimation of enzyme content, in addition to histologic studies, may provide a means of quantitating intestinal function in health and disease.

G 11. *The Use of Fresh $OI^{131}HA$, Purified Product, and Product with Long Shelf-Life in Renal Clearance Rate Studies in Unanesthetized Dogs.* Herman E. Schmid, Jr., I. Meschan, Mohammed S. Navabpour, and Claudius D. Walker (Department of Radiology, Wake Forest College, The Bowman Gray School of Medicine, Winston-Salem, North Carolina)

In a series of 54 renal clearance studies on 18 unanesthetized dogs, it was noted that, although three sequential 10 minute renal clearances employing $OI^{131}HA$ agreed reasonably well with one another, that there was poor agreement on the same dog on different days. Since the non-radioisotopic PAH clearance was stable at this time in these dogs, an investigation was initiated to determine if free iodide was the cause of these spurious results.

A method has been devised (reported elsewhere) for purifying the $OI^{131}HA$ prior to use to delimit the free iodide to 3% or less and sequential studies have been done employing the purified and non-purified $OI^{131}HA$ compound in the same dogs.

The initial results from these experiments would indicate marked differences in the same dog with these two similar compounds—differences which can be reproduced by the addition of free iodide to the purified compound.

Reasonable consistency of results is obtained with the purified compound.

G 12. *The Biologic Fate of Neohydrin-Hg^{203} in Dogs and Humans.* **Harry C. Miller, Jerold P. Green, and Joseph Levine (Divisions of Urology and Radiation Therapy, University of Rochester-Strong Memorial Hospital, Rochester, New York)**

The use of Neohydrin-Hg^{203} as a scanning material has stimulated an inquiry into its biological fate. Using normal and uremic dogs, two microcuries per kilogram body weight was injected intravenously. Daily external measurements of the activity remaining in the kidneys and heart were determined. Urines were collected daily and activity determined by well counting. Three weeks after injection an identical injection was made in the same dogs. Forty-eight hours later the dogs were sacrificed and aliquots of the kidney, liver, muscle, fat, and other tissues were counted for radioactivity. Activity in urine and stool excretions were counted daily in other dogs receiving identical injections. Radioautographs of the kidneys are being developed. Renal function was precisely determined before injection and at completion of the experiment.

By thirty minutes the counts over the kidneys were appreciably greater than over the heart. The maximum counts, at four hours, were halved at twenty-four hours after injection, and again at 4-7 days. Of the total urinary excretion 95% appeared in the first three days. Our figures indicate that a majority of the injected dose is excreted by the kidneys, but about 10% appears in the stool. At forty-eight hours, one-third of the injected dose resides in the renal cortex, 2-3% in the liver, and insignificant amounts in the other tissues. The total dose delivered to the kidney is approximately 20 rads. Radioautographs will demonstrate concentration of isotope in kidney. Total urine and stool excretion is now being studied in patients undergoing renal scanning.

H 1. *Studies of Metastatic Bone Lesions with Sr-^{85}.* **David M. Sklaroff (X-Ray Department, Albert Einstein Medical Center, Philadelphia)**

Strontium-85 localizes sufficiently in bone tumors so that examinations can be made by photoscanning. Metastatic carcinoma and primary tumors have been demonstrated. Its practical application in irradiation therapy will be discussed both in the determination of extent of disease and response to therapy.

H 2. *Magnetic Tape Recording of Scintillation Scan Data.* **Frederick J. Bonte, Jack S. Krohmer, Ernest A. Elmendorf, Stanley E. Hodges, and William E. Romans (Department of Radiology and Medical Electronics Section, University of Texas Southwestern Medical School, Dallas)**

A system has been built permitting the recording of scintillation scan data on two-channel magnetic tape. Raw data are recorded, to be processed selectively at a later time by some such device as a background eliminator. The importance of the rapid replay feature of our circuit will be stressed. The equipment itself will be described in detail, as will the method of operation. Scans of phantom and clinical material will be shown.

H 3. *Correlation of Pre-operative Thyroid Scintigrams and Whole Organ Subserial Sections of the Thyroid Gland Following Total Thyroidectomy in 80 Patients with Thyroid Cancer.* **Michael Ibanez and Raymond G. Rose (Department of Medicine, M. D. Anderson Hospital and Tumor Institute, Houston)**

A review has been made of 82 cases of thyroid carcinoma studied by subserial whole-organ sections, in an attempt to compare the histo-pathologic findings with the preoperative

scintigrams. Correlation was not possible in all cases, due either to lack of scintigraphic study or due to division or undue distortion of the gland during preparation and fixation. In general, tumor nodules of a centimeter or more in size were detectable in scintigrams, but benign nodules and areas of thyroiditis could produce a similar pattern or even obscure evidence of carcinoma. An interesting finding in several cases having multiple minute (1-3 mm sized) cancer nodules was a scintigraphic pattern of diffuse disease in the thyroid. Implications of these correlations as to the value and limitation of scintigrams are discussed. The correlations will be demonstrated by projection of the whole organ thyroid slides and scintigrams in juxtaposition.

H 4. *Technetium-90, As a Biological Tracer.* P. V. Harper, G. Andros, K. Lathrop, W. Siemens, and L. Weiss (Argonne Cancer Research Hospital, Chicago)

Following intravenous administration of carrier free Tc^{99m} as pertechnetate, scans, tissue and secretion studies showed a marked localization in the stomach, salivary glands and thyroid of mice, rats, guinea pigs, rabbits, dogs and man which may be abolished by perchlorate. Blood disappearance curves in dogs and rabbits show a rapid ($T_{\frac{1}{2}}$~8 min) component accounting for about 50% of the injected material and a slow ($T_{\frac{1}{2}}$~6 hr) component accounting for the remainder. The rapid component probably represents localization in the stomach, thyroid and salivary glands and the extra cellular fluid space. The slow component represents urinary excretion and intracellular penetration. Human studies show similar results. The thyroid localization was uninfluenced by the presence or absence of TSH.

The principal gamma radiation of Tc^{99m} is 140 KEV (99%) with no other significant radiation except conversion electrons (10%) and fluorescent X-rays, so that its characteristics are ideal for external scanning with good tissue penetration, ease of shielding and collimation and very low absorbed dose. The activity of the daughter Tc^{99} is negligible. Tc^{99m} is available as the daughter of 2½ day Mo^{99} which is isolated from fission products and may be obtained in 100 mc quantities adsorbed on alumina from which the daughter Tc^{99m} may be milked daily for approximately two weeks with dilute nitric acid. Possible applications are in studies of the "trapping" phase of iodine uptake (~1% of injected dose) in which the pertechnetate ion appears to behave like iodide, and in radiocardiography where the available count rates may be increased many fold without increasing the absorbed dose. Thyroid scans of equal quality to those using I^{131} have been obtained at ½ hour following injection of 1 mc Tc^{99m} with less than 0.1% of the radiation dose.

H 5. *Models and Photoscanning.* D. L. Tabern and G. Dean (Highland Park Hospital, Highland, Illinois)

With the greater resolution and definition made possible in organ scanning through the use of focusing collimators, contrast enhancement and film presentation of data, it seemed desirable to devise a series of phantoms, reasonably approximating each principal scanning area. The second and equally important purpose was to make possible the incorporation of both hot and cold volumes, simulating tumor masses, containing any desired activity and capable of being moved into any position.

Several thyroid systems have incorporated as many as seven "defects", each simulating a clinically observed condition. This has amply demonstrated that photoscanning can detect and delineate nodules, particularly cold ones, smaller than normally palpated by the clinician. It also serves as a valuable training tool.

A plastic system closely simulating the skull has been used to confirm the limited amount of data regarding the extent of Mercury deposition in Brain tumors. It has served as a most useful means of studying collimator design and contrast control settings, enabling adequate data even when counts are as little as 200-250/minute over background.

Work is underway with larger phantoms containing several organs simultaneously, each filled with the appropriate isotope and surrounded by or covered with a medium containing varying amounts of background.

Such studies show that using an appropriately narrow spectrometer window and a 31 hole

fine focus collimator as little as 0.7 uc of either Hg 203 or I-131 can be clearly and quantitatively delineated in a skull containing, in an identical "tumor", as much as 100 or even 1000 times as much activity of the same isotope, and even more if the isotopes are reasonably separable by spectrometry.

H 6. *Some Effects of N-(4-Iodo-Pyrazole-Methyl)-Tetracycline in Animals.* C. D. Eskelson, A. L. Dunn, R. E. Ogborn, and J. F. McLeay (Veterans Administration Hospital, Omaha)

Rall, et.al. and McLeay demonstrated in pretreated tetracycline tumor patients that the tumors could be visualized by means of their bright yellow fluorescence when subjected to an ultraviolet light.

McLeay utilized this phenomenon to attempt to delineate the tumorous areas during surgery, but he encountered difficulties.

A radioactive tetracycline which localizes in tumors would circumvent these difficulties. The quest for a radioactive drug that seeks tumors has resulted in the synthesis of N-(4-Iodo-Pyrazole-Methyl)-Tetracycline which localizes in the liver sufficiently to obtain scintiscans of this organ.

Liver scans from dogs pretreated with the radioiodinated drug will be presented as well as its distribution in mouse tissues (i.e., liver, tumor, bone, blood and muscle).

H 7. *Calibration of a Slit Collimated Scintillation Counter.* Joseph P. Concannon, Roy E. Summers Jr., Norman S. Williams, and Charles V. Mooers (Alleghany General Hospital, Pittsburgh)

An automatic system utilizing a slit collimator scintillation counter combination developed for total body scanning has been employed to determine the size, depth and the activity content of unknown radioactive sources in an absorbing medium. This system includes single channel pulse height analysis, choice of continuous scanning at several speeds or scanning by automatic intermittent motion. The activity is monitored by either a semilogarithmic analogue system or by a digital system.

Calibration of this system makes use of radioactive sources of known activity, physical size and shape, placed at a known depth in an absorbing medium. These sources are scanned by horizontal motion of the slit collimated crystal in the direction of the short axis of the slit, over a source located in the plane of motion of the collimator. A graph of count rate as a function of horizontal position yields gaussion type curves with the parameter h = maximum count rate, h½ = one half maximum count rate and w = the full width of this curve measured at h½. The parameter h is found to vary with the collimator source distance, and the activity and shape of the source, as well as the thickness of the absorbing medium between the source and the crystal. The parameter w is found to vary with the collimator source distance, the size and shape of the source, but is independent of the presence or absence of the absorbing medium and the activity of the source. Since w is essentially a geometrical factor dependent only on collimator source distance and the size and shape of the source, many sources of different size and shape were scanned in air at different collimator source distances.

A study of w as a function of crystal source distance for several known sources in air yields the following findings: (1) w for point sources is a linear function of collimator source distances, the line having a slope greater than zero. (2) Sources with a linear dimension less than 1.85 centimeters behave as point sources at all crystal source distances. (3) Extended linear and circular sources when scanned at large distances behave as effective point sources. (4) Point source and effective point source lines have similar slopes. (5) W is a constant equal to the length of the source, at crystal source distances less than that required for an extended linear source to be seen as an effective point source. (6) The point of change in slope for an extended linear source curve is specific for each length of source. (7) The locus of these points of change in slope is a unique line.

The preceeding information may be applied to the scanning of sources of unknown size, and depth within an absorbing medium. A graph of w as a function of crystal *surface* distance

may be plotted. 1. If the unknown source has a dimension of less than 1.85 centimeters it is seen as a point source. Extrapolation of the line on the crystal, surface distance source graph to zero width determines the depth of the point source within the absorbing medium. 2. If the source has a linear dimension greater than 1.85 centimeters and if w is a constant at several crystal source distance then the length of the unknown source is equal to w. 3. Since the length of the unknown source is now known, the crystal source distance (XID) for the point of change of slope is defined by 6 above. The crystal surface distance (XSD) for the point of change of slope for the unknown, is then measured, depth of unknown source is XID − XSD. We have shown that the depth and size of unknown sources in an absorbing medium can be accurately determined using a slit collimated scintillation counter.

We have also shown experimentally, that for point sources and for linear sources when seen as effective point sources by out collimated scintillation counter system that:

$$\exp\left(\frac{D}{Tm}\right) hw^2 FK = \text{Source Activity} \quad (1)$$

where D is the depth of the source in the absorbing medium, Tm is the mean thickness of the absorbing medium, h is peak counting rate at a specific crystal source distance, w is width at half height. F is an experimentally obtained correction factor for length of source. K is a constant for our apparatus.

H 8. *Anemia, Leukopenia and Thrombocytopenia Following I^{131} Therapy for Thyroid Carcinoma.* Thomas P. Haynie and William H. Beierwaltes (Medical Center, The University of Michigan, Ann Arbor)

Two hundred patients received I^{131} therapy for thyroid carcinoma in the interval September, 1947 to December, 1960 with an average total dose of 186 mc (range 4 to 1142 mc). Complete blood counts were obtained both before and up to 11 years after therapy in 159 patients. Prior to therapy the hemoglobin average in these patients was 13.6 gm% (range 8.8–18.4) and the average WBC was 7.800/mm^3 (3,000–21,650). The average post-therapy hemoglobin and white blood count was 13.7 gm% (6.6-17.6) and 7360/mm^3 (3,200–15,000) respectively.

Subnormal hemoglobin levels (females <12.2 gm%, males <13.4 gm%) were noted after therapy in only 40 patients. In these patients mean hemoglobin before treatment was 13.8 gm% (12.2–16.5) and after treatment 11.2 gm% (6.6–13.2). The average total dose was 310 millicuries (25–1140 mc), and myxedema was induced for periods up to 2 years during therapy. In 32 patients the anemia coincided with this prolonged lack of thyroid. In the 8 patients in whom low hemoglobin persisted, six were females in active menstrual life.

Low WBC values (4,000/mm^3) occurred in 13 patients after therapy. In these patients mean WBC before I^{131} was 5,942/mm^3 (5,000-6,700) and after treatment 3170/mm^3 (2050–3800). The average dose of I^{131} was 498 mc (125-1142). No leukopenia persisted over one year.

Platelets were judged deficient on the peripheral blood smear in 5 patients (from sl↓ to↓↓↓). This occurred after an average dose of 502 mc (70 (+ x-ray therapy) − 1140) and was transient in all cases.

There have been no instances of leukemia or other blood dyscrasia in these patients to date.

H 9. *Thyroid Function Studies in the Newborn.* R. T. Morrison, T. C. Evans, and J. A. Birkbeck (Radiation Research Laboratory and Department of Pediatrics, State University of Iowa, Iowa City)

Previous studies of thyroid function in human newborns have given conflicting results. The normal 24 hour I-131 thyroidal uptakes have been reported as low as 6% and as high as 94%. Studies were made of thyroid function in infants within 36 hours of birth in an attempt to resolve this discrepancy. The following parameters of thyroid function were measured: serial determinations of thyroidal I-131 uptake; *R.B.C. uptake of I-131 labeled T-3* and serum P.B.I. on cord blood. Blood was drawn from the mothers at time of delivery for determination of serum P.B.I. and R.B.C. uptake of I-131 labeled T-3.

In those infants receiving the tracer dose of I-131 intramuscularly the 4 and 24 hour

uptakes were considerably higher than for adults. Those infants receiving the tracer dose of I-131 orally had 4 and 24 hour uptakes in the adult euthyroid range. In both instances time for peak concentration was somewhat later than 24 hours after administration. The high R.B.C. uptakes of labeled T-3 and serum P.B.I.'s were in agreement with those of other workers. The rate of turnover of thyroidal iodine is now under investigation.

H 10. ***Influence of Plasma from a Variety of Stressed Animals on I^{131} Uptake in Chick Embryos.*** **FRANKLIN T. BRAYER (Department of Medicine, Georgetown University School of Medicine, Washington, D.C.)**

The I^{131} uptake in the thyroid of 16 day old chick embryos is significantly elevated 24 hours after exposure to 600 R of x-irradiation. A comparable increase in the thyroidal uptake of I^{131} can be elicited by the injection into untreated embryos of 0.1 ml. of pooled sera from x-irradiated chick embryos, rats, rabbits and guinea pigs. Injection of 0.1 ml. of pooled sera from x-irradiated, thyroidectomized and adrenalectomized rats also elicited a significantly increased uptake of I^{131} in the untreated chick embryo. Pooled sera from x-irradiated, hypophysectomized rats failed to elicit an increased uptake of I^{131} in the chick embryos. Pooled sera from rats exposed to 40 F temperatures for varying periods of time and pooled sera from rats made to swim to exhaustion for five days also failed to elicit an increase in the thyroidal uptake of I^{131} in the chick embryos. The available evidence indicates that the phenomenon is mediated by a substance released from the pituitary gland into the systemic circulation following exposure to x-irradiation.

Research supported by the Public Health Service RH 102 (C1).

I 1. ***Plasma Triolein—I-131 Capacity in Arteriosclerotic Heart Disease—A New In Vitro Test.*** **LAWRENCE W. POLLARD and GUSTAVE F. KILTHAU (Radioisotope Clinic, Internal Medicine Branch, USAF School of Aerospace Medicine, Brooks Air Force Base, San Antonio)**

This technique apparently measures the capacity of serial plasma samples to accept I-131 labeled neutral fat, *in vitro;* of potential predictive value. Well-counting reliably measured activities equivalent to 0.5 micrograms of Triolein-I-131, hence the activity unit (A.U.) was defined as approximating 1.0 microgram (0.001 lambda) of Triolein-I-131 on that date.

A square of filter paper, within a glass tube, was impregnated with about 400 micrograms of Triolein-I-131, washed, dried, and immersed in a plasma sample. This whole unit was counted, the insert removed and the plasma recounted. Normal saline handled identically acquired activity which could be removed by an inorganic iodide binding resin (Squibb-Rezikit) and thus was used to approximate the unbound I-131 expected within the plasma samples. The results (see Table) consistently differentiated between male patients with prior myocardial infarction and age-matched "normal" controls, before and during hyperlipemia induced by oral butterfat (1 gm./Kilogram as 17% cream).

Each individual was studied with an without heparin, on alternate mornings to minimize experimental bias:

Time-After	NO Heparin		WITH 50 mgm Heparin I.V.	
Heparin and/or Cream:	3 Controls:	7 Patients:	Control:	Patients:
Basal (Fasting):	100 A.U.	16.6 A.U.	69.5 A.U.	15.2 A.U.
15 mins:	124.5	13.0	127	30.8
1 hour:	89.5	14.7	166.5	24.7
2 hours:	116.5	14.8	111	28.8
3½ hours:	98.5	13.4	121	22.4
7 hours:	98.5	14.3	102	16.0
24 hours:	114	11.4	71	15.3

In addition to discussing these observations, detailed comments on the technical performance and inherent consistency of this new *in vitro* test of an aspect of neutral fat transport will be discussed.

I 2. *Simultaneous Absorption Studies of I-131-Triolein and I-125-Oleic Acid in the Differential Diagnosis of Steatorrhea.* **MILLARD N. CROLL and DONALD BERKOWITZ (Clinical Isotope Section of the Department of Radiology and the Division of Gastroenterology of the Department of Medicine of The Hahnemann Medical College and Hospital, Philadelphia)**

The use of Iodine-131 labeled triolein and oleic acid for measurement of lipid digestion and absorption has received wide acceptance during the past few years. Since oleic acid is readily absorbed by the normal intestine while triolein must be partially hydrolysed before absorption takes place, one is able to distingiush a defect of digestion from an impairment of absorption by the successive use of the two materials.

Normal technique requires administration of I-131 triolein and the collection of serial blood samples as well as 48-72 hour stool specimens. The second part of the study is similar, but with the substitution of I-131 labelled oleic acid. The total examination requires at least six days for completion.

The recent practical availability of Iodine-125 labeled oleic acid has promoted the possibility of a simultaneous study using I-131 tagged triolein and I-125 tagged oleic acid at the same time in the same patient.

I-125 has a half life of 60 days and emits a 27.4 KEV x-ray and 35.4 KEV gamma ray. With the 80% photopeak of I-131 occuring at 364 KEV, this appears to be a simple spectrometric separation.

This paper examines the practical application of these two isotopes for dual studies. The difficulties encountered with I-125 will be presented and are primarily the result of the self-absorption of the isotope and the need for taking advantage of the "photon efficiency" and lowered radiation exposure for I-125.

A method of counting the mixed samples by integral and differential pulse height analysis will be presented. The importance of determining the constant percentage of I-131 in the I-125 spectral "window" will be emphasized and a technique derived. A series of cases demonstrating the procedure and evaluation of the results will be given.

I 3. *Utilization of Intravenously Administered I-^{131} Labeled Triolein in Normal Patients and Patients with Coronary Artery Disease.* **BENNETT LEVINE and HERSCHEL COHEN (Division of Medicine and Hilda M. Stone Radioisotope Laboratory, Mount Sinai Hospital, Cleveland)**

A relationship between lipid metabolism and coronary artery disease has been accepted. Abnormalities in the blood levels of I-131 labelled triolein following oral administration have been described. These abnormalities include delayed rise and abnormally high and prolonged levels of blood radioactivity. These variations could be accounted for by differences in the rate of absorption or in the rate of utilization of the administered fat.

To measure variations in the rate of utilization of neutral fat, an intravenous fat tolerance test has been devised. This test consists of the intravenous administration of a tracer dose of I-131 labelled triolein to fasting patients. Blood samples were obtained every 20 minutes for 2 hours and then hourly for 8 hours. Total blood radioactivity was counted and then the lipid fraction determined by removal of inorganic I-131 either by dialysis of the plasma or by passage of the plasma through an anion exchange resin column. Values for the lipid fraction were plotted against time on semi-log graph paper. The initial portion of the curve was extrapolated back to zero time and the time needed for 50% of the lipid radioactivity to disappear ($T\frac{1}{2}$) was determined.

Results to date reveal the $T\frac{1}{2}$ for normal controls to average 92 minutes. In patients with proven coronary disease the average $T\frac{1}{2}$ is 190 minutes with very little overlap in values. These results indicate that the utilization of tracer doses of intravenously administered neutral fat is slower in patients with coronary artery disease. The significance of these results will be discussed.

I 4. *Measurement of the Functional Capacity of the Reticuloendothelial System (RES) in Man and Dog.* **Masahiro Iio and Henry N. Wagner, Jr. (The Johns Hopkins University, Baltimore)**

Various doses of a radioiodinated colloidal albumin preparation were administered intravenously, and the rate of clearance of the material from the blood by the reticuloendothelial system was determined. The colloidal albumin was prepared according to the method of Benecerraf, as modified by Taplin and Stern. When temperature of heating, pH, albumin concentration, and amount of shaking were controlled, reproducible results were obtained.

With doses above a critical level, the fraction removed per unit time was inversely proportional to the dose. In studies of 21 dogs and 30 normal subjects, the rate of clearance approached a maximal value of 0.79 mg per minute per kilogram body weight in the dog and 2.03 mg per kilogram body weight in man.

In patients with pneumococcal pneumonia, the mean RES capacity was 50% greater than normal. In patients with Laennec's cirrhosis, the decreased clearance of colloidal albumin at all doses was primarily due to decreased liver blood flow. In patients with hepatic sarcoidosis, the blood flow to the RES was 50% greater than normal, far greater than that observed in other types of portal hypertension.

Measurement of the maximal rate of removal of colloidal albumin is of value in the study of the RES in patients with infections, lymphomas, and diseases of immune mechanisms.

I 5. *Tracer Studies of Reticuloendothelial System (RES) Functions.* **G. V. Taplin, E. K. Dore, E. J. Garcia, G. N. Haddad, and D. E. Johnson (The Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles; and the Nuclear Medicine Division, Department of Radiology of the Los Angeles County Harbor General Hospital, Torrance, California)**

Principles of the methods for measuring liver blood flow, phagocytic and digestive functions of the Kupffer cells are described. The tests are made with heat treated human serum albumin and identical colloidal suspensions of albumin I^{131}. Results of animal and clinical studies are presented to show the potential value of these procedures in the investigation of the role of the RES in diseases of the liver, lungs and spleen and for evaluating the action of steroid hormones, vaccines and pyrogens, which may influence RES functions in man.*

I 6. *Demonstration of Hydatid Liver Cysts with Colloidal Radiogold—International Atomic Energy Agency Scanning Program in Iraq.* **Ralph Adams, A. Y. Hindawi, and Kh. Qassab (International Atomic Energy Agency, Iraq)**

The authors report their experience in the localization of hydatid cysts by liver scanning following the administration of colloidal radiogold.

A high incidence of hydatidosis in Iraq results from unhygenic living conditions and the presence of sheep and stray dogs, fulfilling the requirements for the life cycle of *Echinococcus granulosus*.

The purpose of the project was to demonstrate hydatid liver cysts as an aid in diagnosis and preoperative localization. The authors employed an automatic scanner with three inch scintillation detector and focused collimator, differential analyzer, and digital background

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*These studies were supported by Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California, Los Angeles.

subtractor. Scans were begun thirty minutes or more following the intravenous administration of approximately 500 microcuries colloidal radiogold. Cysts were shown on scintigrams as voids, irregularity of liver contour, or as gross displacement of functioning liver tissue.

The authors present case studies with original scintigrams typical of situations in which scanning has been useful:

1. To rule out liver involvement in cases of known hydatid cyst of the lung.
2. Palpable and enlarged liver, positive seriological tests, but no cystic mass on clinical examination.
3. Cases previously operated, with recurrence of original complaints.
4. Localization of a large cyst displacing functioning liver tissue, to distinguish between cyst and normal tissue as a guide to surgical approach.
5. Clinically suspicious mass but negative seriological reaction.

The authors believe their experience in Iraq demonstrates the usefulness of this procedure in countries where hydatid disease is endemic.

I 7. *A Simple Test to Estimate the Metabolic Effects of Thyroid Hormone.* Tommie Redding and Philip C. Johnson (Department of Medicine, Baylor University College of Medicine and Radioisotope Laboratory, The Methodist Hospital, Houston)

Except for the BMR, thyroid diagnostic tests correlate incompletely with clinical estimates of tissue responsiveness to thyroid hormones. We have used the hexose monophosphate shunt pathway of circulating erythrocytes as a measure of clinical thyroid state and have found that activity in this pathway is depressed after thyroid administration and in thyrotoxic patients. In addition, the degree of this suppression correlates with the clinical severity of thyrotoxicosis.

To perform this test, five ml of heparanized blood is incubated in a 100% oxygen atmosphere at 37° C and in the presence of 5μc of 1-C-14 glucose (0.4 mg of glucose) and 5 mg of methylene blue. The evolved carbon dioxide is collected in hyamine and the C-14 activity measured. C-14 O_2 activity is measured as the percent of the total C-14 added to the vessel.

Blood from euthyroid controls release 10.1 ± 1.4% (mean ± S.D.) of the C-14 as carbon dioxide during the first hour of incubation. Blood from thyrotoxic patients gave 2.9 ± 1.7% (mean ± S.D.). In 5 thyrotoxic patients, six weeks after treatment with radioactive iodine when partial clinical improvement had occurred, the C-14 excretion increased 50% and from 12 weeks on, normal values were obtained in those patients who were euthyroid. Treatment of thyrotoxic patients with propylthiouracil results in a gradual increase to normal values.

This test which is simple to perform, gives an estimate of the metabolic effects of thyroid hormone. To the present, thyrotoxicosis is the only clinical situation which produces this marked depression of glucose metabolism.

I 8. *Placentography.* Millard N. Croll and Larry H. Shuman (Clinical Isotope Section of the Department of Radiology and the Department of Obstetrics & Gynecology, The Hahnemann Medical College and Hospital, Philadelphia)

The first reported use of radioisotopes for the localization of the human placenta was by Browne & Veall in 1950. The next report appeared in 1957, and since then several studies have appeared in the literature.

The purpose of this paper is to report our search for a method of placentography which could be as safe, as reliable, and as convenient as possible.

Safety has been achieved by the use of pre-medication with thyroid blocking agents and the administration of a 5 microcurie dose of I-131 tagged human serum albumin. Radiation

dosage measurement as based upon the study of the post-partum placenta, cord blood, maternal thyroid, peripheral blood and urine, and the fetal thyroid and total body activity reveals an average radiation exposure to the mother of 15 millirads and to the fetus of 6.5 millirads. This compares markedly with the average roentgenographic exposure for two abdominal scout films of 1000 millirads.

Reliability was confirmed in the first 100 patients studied with only one false negative result and the correct evaluation of 24 patients suspected of placenta praevia. Confirmation was made by manual extraction of the placenta or Caesarian Section.

Convenience has been achieved by making this a true bedside procedure. The localization can be performed in the labor room by use of a pre-calibrated syringe of I-131 serum albumin, a small and light weight transistorized scaler, and a hand scintillation probe that is used for external counting as well as intravaginal counting at the cervix. This can be performed as an emergency procedure at night by the Obstetrical Resident on-call with a minimum of training.

Details of the procedure and equipment with presentation of demonstrable cases will be made.

I 9. *Contribution to the Testing of the I^{131}-Triiodothyronine-Uptake by Red Blood Cells.* **J. Foldes and P. Czerniak (Tel - Hashomer Hospital, Israel)**

400 tests were performed with I^{131}-triiodothyronine (Triomet, Abbott Labor.) in women, men and children. The average uptake of I^{131}-T_3 by the RBC was: in euthyroid women–14.3 percent, in men–16%; in thyrotoxic women–22 percent and in men–24.2%; in hypothyroid patients–9.6%. In healthy children the results of the test were in average adult range, without sex difference.

We classified the investigated material in 3 groups:

1). *Ordinary patients* (euthyroid, hyperthyroid, hypothyroid)–in whom the test is considered as an adjunct to other thyroid function tests. The test was in accordance with the clinical diagnosis in 90.0% of euthyroid women and 92 percent of men, in 85.0 percent of thyrotoxic women and in 100.0% of men and in 87.0% of hypothyroid patients of both sexes.

2). *Special patients* (60 cases) includes: a). conditions with artificially increased uptake as: polycythemia, cardiac insufficiency (congestive heart failure), chronic pulmonary insufficiency, nephrosis syndrome, essential hyperlipemia and hypercholesterolemia, following TSH administration, hypothyroid patients treated with thyroid hormone and after giving T_3 (for thyroid "suppression" test.). b). Artificially decreased values were obtained in pregnant women.

3). *Patients for investigation:* The following was studied:

a). The results of the test are influenced by the changes of the hematocrit value shown by the equality $Y = a+kX^2$. A correction should be done, if the Hct is beyond the limit of 35 or 55 percent.

b). Among 3 glutathion defficient anaemic patients, in one case the I^{131}-T_3 uptake of the RBC was increased, According to criss-cross experiments for this effect a plasma factor was responsible. In this patient a haemolysis was observed too.

c). In the early stage of subacute thyroiditis is the I^{131}-T_3 uptake of RBC high, and normalizes 2-3 weeks after the onset of the disease, much earlier than the I^{131} uptake, which is initially low, and normalizes 10-12 weeks after the onset of the disease.

d). After administration of organic iodine compounds, the test yields a reliable index of the thyroid function. 10 patients were daily followed, after a contamination by a contrast medium. Only one showed an increase in the RBC triomet uptake.

e). 8 thyrotoxic patients treated with I^{131} were daily followed, after the intake of the therapeutic dose.

This test might be performed even in this event (background blood radioactivity must be subtracted). It is shown, that the test can serve as a guide in the judgement of the efficiency of the applied therapy.

I 10. *Study of the Liver Using Labelled PVP.* **P. Czerniak, H. Bank, and S. Edelman (Tel-Hashomer Hospital, Israel)**

Labelled PVP was used by Gordon and others for the diagnosis of Enterolosing Hypoalbuminaemia. We performed 107 examinations in 88 patients as also in animals (dogs and rabbits) and besides the foecal excretion we examined the liver uptake and the biliary excretion of the same labelled PVP. Our findings were as follows:

(a) 15-20% of the injected substance is taken up by and remains unchanged in normal livers. 3 pathological hepatic groups could be distinguished: 12 cirrhotics with an uptake of 5-8% only; 4 cases in which the PVP decreases gradually leaving the liver, and 5 cases in which the percent of PVP increased during the first week after injection.

(b) The PVP is excreted into the bile. This was studied in 5 operated gall-bladder patients when a T-tube was inserted into the biliary tracts. The bile was collected in 10 minute samples. We found that the PVP started to appear in the bile within 10 minutes and the maximum was found 60-120 minutes after the injection. About ½% of the injected dose is found in the bile excreted during the first 24 hours.

Dog-experimentation with choledocus fistulae shows a somewhat bigger biliary excretion of PVP I^{131} by the liver of this animal.

(c) The uptake of PVP by the liver was studied by automatic scanning procedure (in rabbits—a hepatoscanning is obtained after i/v injection of 30μc) and by autoradiography.

We conclude: (1) The PVP I^{131}—an albuminlike molecule may possibly be used for diagnosis of special liver disorders (cirrhosis, hyperplastic changes), in which the usual laboratory tests fail to be conclusive.

(2) The existence of an Hepatolosing Hypoalbuminaemiasyndrome can be postulated in which non-metabolised albumins are excreted by the liver into the bile, resulting in a decreasing uptake of the PVP into the liver.

(3) Further autoradiographic studies with labelled PVP possibly may contribute to the elucidation of the pathways of albumin molecules in the liver.

J 1. *Use of Renogram in Renal Shut Down Following Vascular Surgery.* **Arthur Beall and Philip C. Johnson, Jr. (Department of Surgery and Medicine, Baylor University College of Medicine; and Radioisotope Laboratory, The Methodist Hospital, Houston)**

Patients subjected to vascular surgery envolving the aorta, renal or femoral arteries are apt to develop post-operative renal shut down which always creates a difficult clinical situation. Depending upon the cause of this shutdown immediate surgical intervention may be required in a patient who is a poor surgical risk. The I-131 hippuric acid renogram offers a convenient way to determine the etiology of post-operative renal shutdown because the equipment is portable allowing it to be taken to the patient's bed side and because a renogram can be done without anesthesia or the nephrotoxic effects of an aortogram. Using dogs we have found that characteristic renogram curves are obtained after each of the important causes of post-operative renal shutdown. The diagnostic characteristics are as follows:

Renogram phase	*Concentration*	*Excretion*
Transfusion reaction	Slowed	None
Ureteral ligation	Continues throughout record	
Renal artery occlusion	None	None

Our curves are obtained by using 2″ scintillation crystals recessed one inch within a 1″ thick collimator mounted on a portable cart. A scale factor of 300K, a time constant of 0.5 seconds and a dose of 15-30μc of I-131 are used. The detectors can be placed anteriorly or posteriorly. The characteristic curves obtained from our animal experiments and from selected post-operative patients with renal shut down are to be shown and the technical problems inherent in obtaining diagnostic records will be discussed.

J 2. *The Radiohippuran Renogram: Enhanced Reproducibility by Changes in Collimation, Kidney-crystal Distance and Patient Position.* **ROBERT A. NORDYKE (Straub Clinic, Honolulu)**

The radioisotope renogram has become a valuable adjunct in the practice of medicine. Its more widespread use will depend in part on improved simplicity and reproducibility. This requires critical re-evaluation of instrumentation and patient position.

The current renogram technique is left over from the early developmental period when I^{131} labeled Diodrast was the test substance. Since this is picked up in part by the liver, it requires preliminary kidney position x-rays, small collimator apertures and tube tilting with the patient in the sitting position. Reproducible results were difficult to obtain. Great improvement occurred with the advent of labeled Hippuran, which is rapidly removed from the blood only by the kidneys. This allowed certain changes, which we have applied. (1) The collimator apertures were increased to 3″ x 6″ rectangles at the skin surface, allowing each kidney to be viewed in its entirety. (2) The skin-crystal distance was increased to make use of the fact that differences in kidney position make less difference at greater distances. Radioactivity vs. distance curves obtained on a kidney model indicate that the critical skin-crystal minimum distance is 4″. We have chosen 6″ as a safe compromise. (3) Since there is often relocation of the right kidney in the upright position, we have placed the patient in the horizontal position. Extensive clinical trial in the prone position indicated occasional moderate "hang-up" of radioactivity on the right. Subsequent use of the supine position appears to have eliminated this slight defect.

Application of these changes in renogram technique allow comparison of kidney function and excretion with improved accuracy and simplicity.

J 3. *Improved Renal Vascular Evaluation in Hypertension by Means of a Modified I-131 Renogram Method.* **WILLIAM E. WHITE (Research Clinic, Kansas City, Missouri)**

The importance of renal vascular disease as a significant etiologic process in hypertension has emphysized the role of the kidney in blood pressure regulation. Consequently, this study concentrates on determining renal vascular status most simply and efficiently.

The renogram technique employed by Taplan, Winter et al, and Abt and Balkus, has been extended to what will be called here a renovasculargram, which is described as follows.

First, small lead markers are placed on the skin over each renal area and a roentgenogram is made in the prone position. Comparison with the renal shadow is used to determine the center of each kidney.

With the patient again prone, one inch by one inch collimated sodium iodide scintillation probes are placed over the marked areas. I-131 Iodohippurate Sodium (0.5 μc per kilogram body weight) is injected intravenously into the arm and measurements are made simultaneously over both kidneys through a 15 to 30 minute interval, using a dual channel rectilinear recorder.

Count rate measurements are initiated at the moment of injection with the recorder set to move at the rate of at least 0.2 inch per second and maximum response time set between 0.2 and 0.5 seconds, and full scale response set between 30 and 50 thousand counts per minute. Simulating the rate of systemic blood flow provides the renovasculargram.

A characteristic normal renovasculargram sharply delineates circulation time from arm to renal vascular bed bilaterally and usually varies between 6 and 10 seconds. Also clearly indicated is the blood flow up to the renal vascular bed, represented by a rapid rise in radioactivity which reaches a plateau in approximately five seconds. This plateau is then maintained for approximately one minute which completes the renovasculargram. At this point the recorder speed is routinally reduced to a rate of 0.2 inch per minute and allowed to continue for a 15 to 30 minutes to obtain a classicial renogram for evaluation of secretory and excretory function of the urinary tract.

The characteristic renovasculargram for unilateral or bilateral renovascular disease is characterized by minimal to marked prolongation of the arm to renal vascular bed circulation time with unilateral or bilateral prolongation filling of the renal vascular bed with also some reduction in the renal vascular bed due to increased vascular resistance. The interpretation of abnormal renovasculargrams in renal vascular disease was obtained by correlation with confirmatory procedures including angiography, surgery and autopsy.

This two year study is based on one hundred and fifty cases of hypertension and thirty normal controls in age groups 4 years to 80 in which a total of 450 renovasculargrams were carried out.

This technique has provided specific dynamic information regarding the vascular changes in hypertension with and without associated renal vascular disease. In all cases where confirmatory procedures were carried out, this new technique consistently agreed, even in selected cases, eliminating need for angiography. This procedure has also proved valuable as a routine means of evaluating the effects of selected antihypertensive and vasodilating medications employed in the treatment of hypertension and renal vascular disease.

J 4. *Four-channel Magnetic Tape Recording and Digital Integration Analysis of Radio-hippuran Renal Function Tests.* G. J. Hine, M. H. Farmelant, B. A. Burrows, and J. A. Cardarelli (Radioisotope Service, Boston Veterans Administration Hospital and Boston University School of Medicine, Boston)

I^{131}-Hippuran renal function studies have proved useful in detecting gross differences between the two kidneys. Quantitative analysis of individual kidney curves and correlation with such influential factors as urine flow rate, total renal hippuran clearance, or sodium excretion rate has not yet been achieved.

Standard instrumentation consisting of two collimated sodium iodide counters and two rate meters is inadequate to evaluate kidney function quantitatively. If each collimator encompasses a major section of the kidney, at least one third of the count rate results from radioactivity in the tissues surrounding each kidney. This tissue background depends on renal clearance rate and its magnitude relative to the count-rate from radioactivity in the kidney varies as the test progresses. A method of substracting tissue background from the total renal count-rate to yield net kidney counts has been developed.

A body area distance from the kidneys with vascularity similar to the renal fossa area was sought. In a group of 10 nephrectomized patients a third scintillation counter was placed over various body areas and its count rate was compared with that of a counter over the nephrectomized side. Best agreement was obtained from the left infraclavicular area which yields count rates similar to that over the nephrectomized area, except during the first 4 minutes.

Curves obtained with count-rate meters are too undefined when a short time constant is used and too distorted by a long constant, to allow accurate tissue background substraction. Storage of the counter pulses on multi-channel magnetic tape preserves the time relation of pulses from all counters permanently and allows repeated analysis of the data. From the magnetic tape the pulses from one counter at a time are transferred into a 400-channel pulse height analyzer operating in a multi-scaler mode. The time interval of count-rate integration can be selected, between 5 seconds and a fraction of a second. Utilizing the magnetic core memory of the multi-channel analyzer the tissue background counts can be substracted from the total renal area counts for exactly corresponding time intervals and net kidney counts are obtained in digital form. Reading out the data on punch tape allows computer analysis.

With this set-up in operation, correlations between kidney function curves and physiological alterations in the patient are under investigation.

J 5. *Results of a Standardized Hippuran Renogram Review of Two-Hundred and Fifty Cases.* **Robert C. Meade and Donald A. Franklin (Radioisotope Service, Wood Veterans Administration Hospital and Department of Medicine, Marquette University, Milwaukee)**

The Hippuran renogram of hospitalized patients has been evaluated according to a previously established normal range of 78 individuals with no renal disease (Meade and Shy, J. Urology 86:163-170, 1961). Only those renograms which were within the two standard deviation plot were considered normal. In addition, the urinary excretion of Hippuran in the first 30 minutes was determined, by well counting of a diluted 30 minute urine specimen and comparing with the administered dose. In many cases, a Hippuran cystogram was done to determine residual urine.

The results of the first 250 renograms were compared to clinical and laboratory evaluation including urinalysis, PSP excretion, urea clearance, blood urea nitrogen, intravenous and retrograde urography, aortagraphy, renal biopsy, individual kidney excretion studies and autopsy findings.

Sixty-two per cent of the total patients had an abnormal renogram. Sixty-nine per cent of 91 cases referred for hypertension were abnormal. A diagnosis of renal disease was made in eight of the patients with a normal renogram (8%). The average 30-minute Hippuran excretion was 64.5% in the normal patients. Abnormals show consistently lower values, going down in extreme cases to a few percent. This compares to 67% originally established in the 78 normal individuals. The average BUN associated with normal renogram was 13 mg% and never exceeded 20. In the abnormal studies, decreased Hippuran excretion correlated well with elevation of BUN.

Wtih the exception of renal carcinoma, congenital absence and nephrectomy, the abnormal renogram showed a bilateral defect in all except 13 cases. Unilateral kidney disease was supported by other diagnostic procedures in 9 and hypertension was significant in 10 of the 13 cases.

All patients with an abnormal renogram had evidence of urinary tract disease by at least one other test with the exception of 3 cases and in 2 of these, obstruction demonstrated by renogram was associated with persistent pyuria. In certain disease states there appears to be a rather consistent renogram abnormality.

There was good correlation between the Hippuran renogram and other kidney function tests. A comparison of diagnostic accuracy of the various procedures will be presented. As a single test of renal function, the Hippuran renogram combined with the 30-minute Hippuran excretion study, exceeded the accuracy of the other tests performed.

J 6. *Correlative Clinical Studies with the Hippuran Renogram.* **William G. Battaile, Hector J. Salazar, and Oscar B. Hunter, Jr. (Oscar B. Hunter Memorial Laboratory, Washington, D. C.)**

The Hippuran renogram requires accurate standardization of both dosage and instrumentation to obtain comparable results. Normal values have been established from studies of almost 100 individuals. Correlation studies were done to identify the nature of abnormal renograms. These consisted of a urinalysis, BUN, creatinine and IV pyelogram.

It seems apparent that the radioactive renogram is a good screening test for renal disease. This is particularly applicable to cases of suspected unilateral renal disease. The test is easily performed and offers virtually no hazard. This test requires no urinary tract instrumentation. At present, it is impossible in all instances to differentiate renal insufficiency as to its etiologic cause. The renograms obtained from patients with renal artery disease, glomerular disease, renal tubular disease and obstructive disease are frequently similar. The procedure is not of limited usefulness in establishing prognosis.

J 7. ***An Approach to the Standardization of the Isotope Renogram.*** **W. Newlon Tauxe (Section of Clinical Pathology, Mayo Clinic, Rochester)**

Since the isotope renogram has proved to be an effective qualitative screening device, it is now necessary to establish its range of normal variations in order to facilitate interpretation of its curves.

On the basis of 74 renograms made under standardized conditions in normal subjects, we have determined the ranges of normal, the limits, and the maximal differences between values of the two kidneys, under conditions of hydration as well as of relative hydropenia. With this system, information given by the isotope renogram may be reduced to a set of six easily derived index values which effectively separate abnormal from normal curves. These indices have been designated the vascular, parenchymal, parenchymal rise, peak time, and 20 and 30-minute evacuation indices.

Of 94 patients who underwent renal arteriography and classic separate-function clearance studies, 54 proved to have renal arterial disease on the basis of these tests. A renogram utilizing radioiodinated ortho-iodohippurate and standardized by this technic proved to be abnormal in every one of the 54 cases. There were no false positive tests.

J 8. ***Current Radiorenocystogram Interpretations.*** **E. K. Dore, D. E. Johnson, G. N. Haddad, and G. V. Taplin (The Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles; and the Nuclear Medicine Division, Department of Radiology of the Los Angeles County Harbor General Hospital, Torrance, California)**

The limitations of renocystograms are described along with those of standard methods for evaluating individual renal functions. Original interpretations are modified. The physiological basis of normal renocystogram dynamics is clarified. New concepts and terminology are developed from analysis of the effects of fluid restriction and loading doses of para-aminohippurate (PAH) on renocystogram dynamics. The tubular segments are now called tubular transport segments to imply a close relation between blood supply and cellular function and a time factor for movement of tracer from the blood into the cells and secretion into the collecting tubules. A new concept of minimum tubular transport time is developed and its relation to urine flow is described. Recent clinical experience with renocystograms in chronic pyelonephritis and occlusive renal artery disease is presented to demonstrate the diagnostic value of current concepts of renocystogram interpretations.*

J 9. ***Renocystograms and Intravenous Pyelograms.*** **G. V. Taplin, E. K. Dore, D. E. Johnson, T. T. Tan, and G. N. Haddad (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles; and the Nuclear Medicine Division, Department of Radiology of the Los Angeles County Harbor General Hospital, Torrance, California)**

Interpretations from the two procedures are analyzed regarding individual renal function in 100 patients. In all instances both procedures were performed no more than a week or two part. Diagnoses included pyelonephritis, renal arterial disease with hypertension, essential hypertension, and various forms of nephritis and obstructive uropathy. The physiological and technical differences between procedures are discussed in relation to the paradoxical finding (by IVP) of greater radiodensity in the *affected kidney* in unilateral occlusive renal artery disease and in some patients with pyelonephritis. The physiological basis for this paradox is clarified with the renocystogram. The value of interpreting one procedure in the light of the other is stressed.

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J 10. ***The Radioisotopic Renogram in Renovascular Hypertension.*** **JAMES L. QUINN, III (Department of Radiology, North Carolina Baptist Hospital, Winston-Salem)**

The radioisotopic renogram has become an important diagnostic tool in hypertensive screening. In combination with the intravenous urogram candidates for renal arteriography are better chosen.

Modifying the conventional renogram by accelerating the initial vascular phase until it plateaus and monitoring the aortic bolus with a third probe anteriorly, valuable information is obtained.

Fifty cases of hypertension were evaluated by intravenous urography, renogram and arteriography. The renogram detected and lateralized significant arterial disease more accurately than the excretory urogram. Bilateral renal artery stenosis, missed by urography, was detected by renogram. The renogram is helpful in evaluating the patency of renal artery grafts in the immediate post-operative period.

In at least six cases the only renogram abnormality, with renal artery disease, was in the accelerated vascular phase.

A delay in the peaking of the vascular phase, as compared to the aortic probe, of 33-42% (2 S.D.) is suggestive and 42% (3 S.D.) or more definitely abnormal and indicates decreased renal vascular flow.

A difference of vascular plateau height or 20-25% (2 S.D.) is suggestive and greater than 25% (3 S.D.) definitely abnormal, providing good probe localization, of unilateral decreased functioning renal mass.

This method is not without limitations and the criteria for interpretation of the accelerated vascular phase with its attendant pitfalls will be discussed.

A significant number of vascular phases will be uninterpretable because of lung, aortic or flank interference. Renal function, diminished to 15-20% or less will be undetectable. Renal infarction, unless massive, will be missed by the renogram.

K 1. ***Some Applications of Activation Analysis in Medicine.*** **RICHARD E. OGBORN (Radioisotope Service, Veterans Administration Hospital, Omaha)**

The role of elements in human metabolism is at present little understood and difficult to investigate. Since the early work of Dr. Tipton in establishing element levels in normal tissues, there has been an increase in the investigation of the role of elements, per se, in the disease state. A corollary investigative program is the attempt to formulate the role of metals in enzymatic systems of the human organism. The chelating effects of metals is under intensive study, as well as the effects of chelates on metals at cellular levels. Previous to neutron activation analysis and x-ray crystal spectrometry, the technics of measurement for many of the trace elements have not been adequate to accurately measure the minute quantities present in human specimens. A cursory review of the broad program of adapting neutron activation analysis to the medical sciences as well as the specific program under way at the Omaha V.A.H. will be presented.

K 2. ***High Speed Activation Analysis Systems for the Analysis of Biological Materials.*** **R. E. WAINERDI, D. GIBBONS, and L. E. FITE (Activation Analysis Research Laboratory, Agricultural and Mechanical College of Texas, College Station)**

Activation analysis is based on the principle that when a material is irradiated by the nuclear particles produced in a nuclear reactor, particle accelerator or other suitable source, some of the atoms present in the material will interact with the bombarding particles and be converted into different isotopes of the same element or isotopes of different elements, depending on the nature of the bombarding particles. In many cases, the isotopes produced are radio-

active. If each different induced radioactivity can be distinguished or separated from all other radioactivities present, then the amount of each radioactivity is a measure of the quantity of the parent isotope present in the material.

The Activation Analysis Research Laboratory is engaged in a study of computer coupled automatic activation analysis as a routine analytical tool, under contract with the Division of Isotopes Development, United States Atomic Energy Commission. This investigation has included the development and construction of an automatic gamma ray spectrometer with automatic sample handling and automatic data processing facilities (the Mark I system). Various IBM 704 and 709 digital computer programs have been developed for use with the system, ranging from the extremely complex, capable of analyzing unknown samples, to the relatively simple, capable of rapidly analyzing a sample about which some preliminary information is already available.

The Laboratory is now building a high speed, magnetic tape coupled, automatic activation analysis system (the Mark II system). This device is designed for the analysis of up to 2,000 samples per day when the system contains four analyzers and detectors, and this number can be increased by the addition of analyzers and detectors. This will permit large scale "surveying" of blood, urine, and tissue. One of the first applications of this device will be in an attempt to diagnostically correlate trace element abundances.

K 3. *Specific Problems in Neutron Activation for Trace Metal Analysis in Human Serum.* THEODORE FIELDS, E. KANABROCKI, E. KAPLAN, and S. BRAR (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois; and Argonne National Laboratory, Argonne, Illinois)

Subsequent to recent publications by this laboratory concerning the use of neutron activation to problems of determination of protein bound metals in human serum, a number of improvements in techniques, analysis and equipment have been made.

Sample preparation has been improved by use of ion exchange resins used in demineralizing the water in buffer preparation; smaller volumes of buffer used in dialysis; more efficient dialysis with magnetic stirrers; and use of larger serum sample volumes.

Activation time has been increased to one-half hour still keeping the procedure a cold lab technique. Counting is now being performed on a 512-channel analyzer reading out into a punched tape. Read-in and read-out can be done simultaneously. Analysis of data is done by procedure of D. F. Covell (Anal. Chem., Vol. 31, 1785-1790, 1959).

Preliminary data indicate new values observed in normal adult male subjects of protein bound Manganese in serum averaging about 1.6 micrograms per 100 ml. serum. Average values of protein bound Copper in serum were found to be 137.7 micrograms per 100 ml. serum in the same group of subjects.

Analyses were made on patients with recent myocardial infarcts and comparison made between protein bound Manganese levels and SGO-Transaminase values.

Results will also be presented on tests made on normal and abnormal human spinal serum.

K 4. *Determination of Mg. Mn. Zn and Copper in Human Blood by Activation Analysis.* W. F. BETHARD, R. A. SCHMITT, and D. OLEHY (General Atomic Division, General Dynamics Corporation, San Diego)

Although certain trace elements are known to be important co-factors in essential biochemical reactions, investigation of their precise roles has been hampered by the small quantities of elements required and by inadequate macrochemical techniques. A prime example is that of magnesium. Magnesium is extremely important not only clinically where gross deficiency results in definite symptoms, but also in specific biochemical processes demonstrated by in vitro techniques. Magnesium is a necessary co-factor in a majority of the steps of the Emden-Meyerhof scheme of anerobic glycolysis. The functional integrity of many organs is dependent upon energy obtained from such glycolysis. Analytic methods for magnesium have improved, but biological concentrations continue to tax the limits of their precision. To this problem has been

applied neutron activation techniques. Specifically, an effort is being made to determine whether or not loss of magnesium from erythrocytes during blood bank storage contributes in any measure to loss of cell viability. Parallel studies are underway for manganese, copper, and zinc as well. The present program endeavors to apply neutron activation analysis techniques to a few highly important trace elements in specific clinical or biochemical situations rather than to determine the total "profile" of all trace elements present. Ultimately both approaches are necessary.

K 5. ***Activation Techniques with a Portable 14 Mev Neutron Source.*** **HOWARD I. OSHRY (Lane-Wells Company, Houston)**

Preliminary experiments carried out with a portable source of 14 mev neutrons indicate that fast neutron activation even with moderate flux densities offers a useful technique for identification and nondestructive analysis of the lighter elements.

The analysis technique requires irradiation of the sample followed by measurement of both the radioactive decay rate and the spectral characteristics of the induced radioactivity. Neutrons produced by the $T(dn)He^4$ reactions are emitted by a small self contained ion accelerator which is used to bombard a small sample of the material to be analyzed. A scintillation spectrometer is used to analyze the induced activity as it decays away.

The method is most successful for those elements which produce radioactivities with half-lives ranging from a few seconds to a few hours. This includes some elements which are not readily detected by conventional activation analysis techniques, such as oxygen, silicon and nitrogen.

The short-lived radioisotopes produced by fast neutron activation may also be employed as low level tracers to follow the movement of materials in inaccessible places. For example, the flow of oxygen-containing liquids can be traced by irradiating the fluid and detecting the resultant N^{16} which is a 7.3 second beta-gamma emitting isotope produced by bombardment of oxygen. A small, low power, portable source has been found particularly advantageous for measurements of this type.

K 6. ***The Armed Forces Radiobiology Research Institute.*** **JAMES F. BRENNAN (Armed Forces Radiobiology Research Institute, National Naval Medical Center, Bethesda, Maryland)**

K 7. ***Computers in Activation Analysis.*** **BARNEY T. WATSON (Radioisotope Service, Veterans Administration Hospital, Omaha)**

The basic assumption in our Neutron Activation Analysis System is that the spectra of activation elements in a compound add linearly. If the assumption is true, then the proportionate parts of a composite spectrum may be assigned to the proper elements by solving a set of simultaneous linear equations of order (k) of the number of radioactive elements in the composite. A matrix solution to such a set of equations may be defined as follows:

$$\begin{vmatrix} a_{11} & a_{12} & a_{11} \\ a_{21} & a_{22} & a_{21} \\ \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots \\ a_{k1} & a_{k2} & a_{k1} \end{vmatrix} \begin{vmatrix} b_{11} \\ b_{22} \\ \cdots \\ \cdots \\ b_{kk} \end{vmatrix} = \begin{vmatrix} N_{11} \\ N_{22} \\ \cdots \\ \cdots \\ N_{kk} \end{vmatrix}$$

The a_{k1} are ratios defined as $a_{k1} = \frac{n_{1k}}{n_{11}}$, where n_{1k} is the number of counts of the i(th) element at energy k. The values of a_{k1} are determined from the standard spectrum of each element in the composite

The b_{11} values are the total counts of the composite spectrum in the energy k of each ele-

ment in the composite. The resulting N_{kk} are the counts due to each element in its own energy k. These N_{kk} may then be compared to the counts of the standard (N_{kk}:MASS::COUNTS:STD MASS) so that $\text{MASS} = N_{kk} \frac{\text{STD MASS}}{\text{COUNTS}}$.

The method of computing N_{kk} from the basic matrix is to compute the inverse of the a_{kj} matrix and then multiply the sum of each row k of the inverted matrix times the counts b_{kk} for that row. These products are N_{kk} that may be used in the formula $\text{MASS} = N_{kk} \frac{\text{STD MASS}}{\text{COUNTS}}$ to get the masses of the k elements in the composite.

A 3×3 numerical example will be presented. There are basic limitations to such a method of solution. One, the order of magnitude of the ratio of the least active to the most active element must not exceed 10^3. Two, all elements in a given sample composite must be known and must be in your library of standards.

K 8. *The Use of a Nuclear Reactor in Activation Analysis.* ALAN J. BLOTCKY (Radioisotope Service, Veterans Administration Hospital, Omaha)

During the past few years many articles have appeared on the subject of Neutron Activation Analysis but little has been said about the actual techniques of preparing, irradiating and counting the samples.

Since the program which is being developed at the Omaha Veterans Administration Hospital involves nondestructive activation analysis of trace elements using a library of standard spectra rather than comparison samples, it is of utmost importance that all variables in the activation analysis formula be kept either constant or normalized so that the unknown samples can accurately be compared with the standards.

Procedures for maintaining a constant neutron flux, obtaining accurate weighings, and insuring reproducible irradiation time will be outlined.

In addition, it has been found that sample preparation and selection of proper irradiation containers are very important factors in obtaining reproducible results since any trace amounts of contaminants will be activated and consequently add to the spectrum. Examples of these effects will be shown.

Another problem to consider is the activation of air that might be contained in the vial. In the present method being used, samples are counted after a nine-minute cooling time. Since N^{16} has a 7.4 second half life, the amount detected is insignificant. O^{18} also has a comparatively short half life of 29 seconds so that its contribution is also insignificant. Argon, however, comprises 1% of air, its precurser is 99.60%, and it has a half life of 109 minutes. It has a 1.29 Mev Gamma, which contributes quite a bit to the spectrum. A technique will be described which enables the Argon contribution to a 2 ml sample of water to be reduced from 1120 counts/min to 2 counts/min.

K 9. *Application of Activation Analysis to Various Trace Elements.* ARTHUR L. DUNN (Radioisotope Service, Veterans Administration Hospital, Omaha)

The technique of activation analysis is based on the formation of radioactive nuclides through transformation or transmutation of the trace elements of interest by reaction with nuclear particles. In the case where thermal neutrons from a nuclear reactor are the particles in question the usual reaction is "neutron in; gamma out" and there can be formed about 220 possible different radio nuclides.

The application of this type of activation analysis to the estimation of trace elements in blood serum is discussed. For some elements the method offers no particular advantage; for other the sensitivity is so great that neutron activation analysis becomes a very powerful tool. The feasibility of this method when applied to the trace elements in serum is discussed. The problem of measuring minute quantities of many elements in the presence of relatively massive quantities of sodium and chloride is explored. Several approaches are described which include electronic, computer and radiochemical techniques.

The reconciliation of two very different points of view which arose in the field of neutron activation analysis is mentioned. Whereas, early workers in the field held that radiochemistry was the procedure of choice in the isolation and quantitation of trace elements, later, the feeling grew that totally automated analytical schemes were the answer. Present thought seems to point out that a combination of the two techniques, tailored to the job at hand, holds the greatest promise.

T 1. *The Rate of Incorporation of P^{32} Adenine Nucleotides of Erythrocytes from Normal and Schizophrenic Subjects.* **Joseph Bernsohn, James T. Gustod, Alexander P. Remenchik, and Peter J. Talso (Neuropsychiatric Research Laboratory, Veterans Administration Hospital, Hines, Illinois)**

A multidisciplinary investigation of schizophrenia is in progress at this institution. The biochemical studies have included the measurement of the rate of incorporation of P^{32} into the inorganic P, adenine nucleotides, diphosphopyridine nucleotide and hexose diphosphate of erythrocytes. The patient group consisted of recently admitted subjects diagnosed clinically and psychometrically as being schizophrenic. At the time of phlebotomy, the only medication received by the patients was chlorpromazine. The control group consisted of hospital and laboratory personnel.

Ten ml. of whole blood was incubated with 10 μc of carrier-free P^{32} as the orthophosphate, and samples placed in a Dubnoff incubator for 20, 40, 60 and 120 minutes at 37°C. It was found that the specific activities (Cts/min/μmole P) of the ATP fraction was lower at all the time intervals studied for the schizophrenic subjects, indicating a diminished turnover for this compound, which was statistically significant at 120 minutes. In addition, the specific activity for ADP was also decreased in the schizophrenic group while the inorganic P and weak-acid phosphate compounds specific activity showed no significant changes. Accompanying these changes in specific activity, it was found that the ATP levels increased during the incubation period in the schizophrenic population. Since the energy derived from glucose utilization is available via high-energy phosphate bonds, the changes observed would be consistent with the concept that the decrease in turnover rate in ATP is the result of a diminished requirement for these high-energy bonds because of the non-utilization of available energy.

T 2. *The Long-Term Component of Sr Turnover in Man.* **S. H. Cohn, H. Spencer, J. Samachson, and J. S. Robertson (Medical Research Center, Brookhaven National Laboratory, Upton, Long Island)**

Determination of the biological turnover of Sr over the span of a human lifetime is limited by the relatively short half-life of the gamma-emitting tracer, Sr^{85}. It therefore becomes necessary to express turnover data by means of a suitable mathematical model, in order that extrapolations may be made over relatively long periods of time as compared to the period of actual measurement. Long-term retention of Sr^{85} was measured in this study in 6 patients for a period of a year, and expressed both as a series of exponential functions and as a power function.

Both the exponential and the power functions describe the data accurately for the period of measurement. However, projections of these functions over 40 years produce values which diverge widely. The exponential function appears to be unsuitable for such long-term projection; therefore, it becomes necessary to employ the power function for the estimation of Sr retention at 40 years following administration of the isotope. Working back from the value so obtained to determine the value of the more familiar concept, half-life, it was calculated that the long-term exponential component that would produce this value has a half-life of 110 years.

T 3. *Radioisotope Liver Coefficients, Using the Liver Scintillography.* P. Czerniak (Tel - Hashomer Hospital, Israel)

The three-planes scintillography of the liver after Au^{198} injection, using a cliniscanner, allows us to conclude, if we have:

1) A normal liver
2) Topographical liver changes
3) Space occupying liver lesions
4) Spleno- hepato- visualization

and

5) Foggy livers

The foggy pictures are obtained in cirrhotic, carcinomatous metastatic infiltration and in other infiltrative diffuse changes. It is of clinical importance to distinguish between cirrhotic and multimicrometastatic liver. This cannot be done from the hepatoscanning only. We performed the following: The patients were weighed (in kg.), the hepatoscans were measured (in cm^2) and the radioactivity emitted by the liver during the scanning procedures was counted by a scaler. All the examinations were performed in standard conditions. We calculated 2 coefficients:

$$\text{The area coefficient} = \frac{\text{Scan-area}}{\text{Body weight}} \left\{ \frac{cm^2}{kg} \right\}$$

and the

$$\text{radioactivity coefficient} = \frac{\text{counting}}{\text{scan area}} \left\{ \frac{\text{cts}}{cm^2} \right\}$$

It was found as follows: in normal cases the area coefficient equals about 2 in ap., lat. and pa. position and the radiation one = 125 (with our instrumentation). In cirrhotic livers: the area coefficient is unchanged, the radiation one is lower.

In metastatic infiltrative liver: the area coefficient is elevated and the radiation one is lower.

The results of these radioisotope liver coefficients were confirmed by objective tests.

T 4. *A Method for Studying Fe Absorption Using Ferrous^{59} Sulfate Tablets.* Miguel A. Escobar, Alessandro Emanueli, and Frank E. Trobaugh (Section of Hematology, Department of Medicine, Presbyterian-St. Luke's Hospital; Department of Medicine, University of Illinois College of Medicine, Chicago)

Intestinal absorption of radioactive iron has been studied by measuring the incorporation of orally administered Fe^{59} into the circulating red blood cells.

Two different pharmaceutical preparations of ferrous sulfate were tested. Iron deficient patients and control subjects with normal serum iron and peripheral red blood cells were studied. Two tests were performed on each subject in an attempt to provide measures of within subject variation and any residual effects. Each subject received two test doses in the order selected from a prepared table of randomization.

It was assumed that the rate of erythrocyte incorporation of plasma iron would remain constant in the same individual during the four week period of the experiment. Any differences noted in the red blood cell incorporation of orally administered iron between different tests on the same subject were assumed to be due to differences in intestinal absorption.

The red cell mass of each individual was determined using Cr^{51} sodium chromate. One hundred and five mg of ferrous sulfate containing 25 microcuries or less of Fe^{59} were administered orally to a fasting subject. Fe^{59} activity of the peripheral blood was determined three times weekly until the plateau of iron incorporation in red blood cells was reached. At that time the proportion of the administered iron absorbed was determined by referring the total circulating Fe^{59} to the amount administered.

At this time, study has been completed on 16 iron deficient patients and 9 control subjects.

Details of the technique, including the selection of subjects and the corrections made for variation of isotope content between tablets will be presented.

T 5. *Experimental Study of a Specific Emotional Stress on Hyperthyroid Patients.* **Glenn W. Flagg (Psychiatric Research, Mount Siani Hospital, Los Angeles)**

Previous work on the emotional factors which serve as a "trigger" in the precipitation of thyrotoxicosis has shown that the hyperthyroid patient has a specific emotional vulnerability characterized by: Extreme emotional deprivation as a child due to death of parental figures, rejections or violence—to which the child has reacted with a premature need for self-sufficiency and maturity by denial of his dependency and manifested in behavior by counterphobic attitudes and taking care of others. The major characterological patterns of these patients serve to deny fear by repression and ambitious work behavior. In this present study, a dramatic film is chosen which contains as its main theme the identical conflict with which the thyrotoxicosis patient is struggling and is shown to a group of treated and untreated hyperthyroid patients and a series of controls. The subjects are given objective psychological tests before the exposure to the film, and these psychological tests and also psychiatric interviews are conducted for a follow-up period after the movie. The level of thyroid response is measured by PBI 131 blood levels taken before and at hourly intervals after the film, as well as chemically determined PBI. Continuous neck counts are taken during the film exposure and at hourly periods after the exposure. Autonomic parameters are measured by GSR, plethysmogram, cardiotachometry, respiration rate, electromyography and continuous blood pressure recording. We hope by this investigation to study in more detail psychophysiological correlations in the above group of thyrotoxics as compared to control groups.

T 6. *The Effects of Certain Drugs on the Uptake of T3 by Erythrocytes.* **Walter DiGiulio, Moulai Benmiloud, and George E. Thoma (Section of Nuclear Medicine, Department of Internal Medicine, St. Louis University School of Medicine, St. Louis)**

Employing Hamolsky's method, the effect of certain drugs on the uptake of I^{131}-labeled T3 by erythrocytes was studied. Samples containing various concentrations of drugs were prepared by the *in vitro* additions of the drugs to whole blood.

Significant elevations in the red cell uptake were noted in blood containing therapeutic concentrations of sodium salicylate and phenylbutazone. The T3 uptake was not significantly affected by therapeutic concentrations of testosterone, diphenylhydramine, warfarin sodium, estrogen, or phenylindanedione. Combinations of these drugs, however, did have sufficient additive effect to cause significant changes in the uptake.

It is postulated that salicylate and phenylbutazone strongly compete with thyroid hormones for the protein-binding sites. The other drugs tested individually are incapable of replacing hormone to a degree sufficient to alter the red cell uptake to the extent necessary to be significant for the method employed.

T 7. *The Radioactive Phosphorus Test in Ophthalmology.* **Bernard Goldberg, David Tabowitz, Gerald B. Kara, Saul Zavell, and Romeo Espiritu (The New York Eye and Ear Infirmary, New York)**

The ability of newly proliferating cells to concentrate P^{32} is the basis for a clinical test wherein the differential uptake of radioactive phosphorus is utilized to differentiate benign from malignant ocular lesions. The inability of the eye to withstand biopsy procedures makes it imperative that supplementary data be obtained which will confirm the clinical impression which is based primarily on observation. Inasmuch as the diagnosis of intraocular tumor makes it incumbent upon the surgeon to enucleate the affected globe, the ophthalmologist welcomes the additional information provided by the P^{32} test. The use of this test has improved the accuracy of the ocular tumor diagnosis and decreased the loss of potentially useful eyes.

The paper contrasts the external approach for anterior segment lesions (iris, ciliary body and anterior choroid) with the transconjunctival approach for posterior segment lesions (posterior choroid). The significance of scanning, recent surgery and the 48 hour determination are discussed. The findings in a series of 225 patients are summarized.

T 8. *Large Particles of Yttrium-90 to Treat Advanced Cancer.* **EDGAR D. GRADY, WALTER SALE, and LUTHER C. ROLLINS (Atlanta, Georgia)**

Yttrium oxide was fused at high temperature, crushed and seived to form particles slightly larger than capillaries. These were then converted to Y-90 and suspended in 12% dextran to inject into blood vessels of rabbits and dogs. When renal arteries, portal veins or femoral arteries were injected, the majority of the material was found to be distributed homogenously throughout the organs supplied by the vessels. If internal carotid arteries were injected, little was found to lodge in the brain. When intravenous injections were made, about 70% was homogenously distributed throughout both lungs. No damage was done in any case.

Twelve patients with advanced cancer in lung, liver or pelvis have been treated. Homogenous distribution and effective radiation without ill effect have been demonstrated in most cases. The usual dose was 6 millicuries per kilogram total body weight.

T 9. *Factors Influencing Triiodothyronine-Resin Binding.* **C. HLAD, M. ERVIN, S. GUGGENHEIM, and H. ELRICK (V. A. Hospital and General Rose Memorial Hospital, Denver)**

During the past few years, there has been much interest in the development of an *in vitro* test for tyhroid function. The triiodothyronine-erythrocyte binding procedure has been studied extensively but due to errors inherent in the system, is has not gained wide-spread acceptance. The authors previously reported a study of these errors. Since there was no apparent way of correcting for the error due to hematocrit variation, it was decided to investigate means of eliminating it entirely. This paper reports experiments using a resin (IRA-400) to replace the erythrocyte as a binding site for triiodothyronine. We have found that IRA-400 is adequate for binding triiodothyronine in aqueous solution, plasma and serum.

In contrast to the erythrocyte binding system, it was found that certain anticoagulants had a marked effect in the resin system. Heparin, citrate and EDTA resulted in a decreased binding of triiodothyronine to resin (11 to 66%), depending upon the amount of anticoagulant. Oxalate caused decreases of only 2%. In all cases serum resulted in greater resin uptakes than plasma.

The relative amounts of serum and resin had a marked effect on the resin uptake. Dilutions of serum ranging from 10 to 90% resulted in resin uptakes from 75 to 30%. Variation in the amount of resin from 10 to 100 mg. resulted in variation of resin uptakes from 20 to 80%.

The temperature and time of incubation was studied. From 25 to 40° C. there was an increase of 1.4% in the resin uptake per degree C. Increasing the time of incubation resulted in an increased uptake on the resin, and a plateau was not reached in 3 hours.

The information from these studies has been used to derive a method for the measurement of thyroid function. Experience with this test in 75 patients will be reported.

T 10. *Study of T_3 and T_4 Binding to Glass and Electrophoretic Filter Paper Using a Dis-equilibrated Dialysis Technique.* **JOHN J. IMARISIO, JOSEPH GRECO, and ERVIN KAPLAN (Radioisotope Research Section, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)**

To study the characteristics of Triiodothyronine (T_3) and Thyroxine (T_4) binding to glass, electrophoretic filter paper and proteins, the previously described continuous flow, constantly monitored, dis-equilibrated dialysis system was employed.

The amount of radioactive T_3 of constant specific activity adhering to constant bore, uniformly sized pyrex test tubes exposed to 0.1 μgm T_3I^{131} in a 5 ml. volume, after a single washing of the tubes using 5 ml. isotonic saline was found to be relatively constant; (0.01 μgm) T_3 regardless of the time the T_3 was exposed to the glass.

Test tubes exposed to T_3I^{131} for one minute, at the end of an hour of continuous flow wash with isotonic saline, had 0.001 μgm residual T_3I^{131}; those exposed for 30 min. had 0.0024 μgm;

the tubes exposed for 60 min. 0.0038 μgm; those exposed for 24 hours 0.0065 μgm; showing that the time of exposure significantly influenced the tenacity of the glass-hormone binding. The longer the exposure the greater was the tenacity of binding with flow wash, but the curves suggest that a plateau is reached where the glass becomes saturated between 2 and 24 hours.

Studies in progress will test ways of eliminating, minimizing, or controlling glass-hormone binding in quantitative studies.

Electrophoresis filter paper was carefully loaded with a fixed dose of T_3I^{131} and T_4I^{131} utilizing the capillary action of the dry paper. T_4I^{131} was found to bind more tenaciously to the filter paper than did T_3I^{131} when flow dialyzed in a Visking bag. NaI^{131} used as control showed no binding.

The different protein segments of the electrophoretogram of 20 lamda of serum (veronal buffer) were separated and similarly spiked with T_4I^{131}, allowed to dry, cut into small strips and dialyzed in a Visking bag in the flow dialysis system.

Both the albumin-T_4I^{131} and alpha-globulin T_4I^{131} complexes on filter paper dialyzed more slowly than the albumin-T_4I^{131} or alpha-globulin-T_4I^{131} complexes in solution. Gamma-globulin-T_4I^{131} complex which is very loosely bound showed very fast dissociation in solution but when the gamma-globulin-T_3I^{131} on filter paper was flow dialyzed a marked slowing in the rate of dialysis of the dialyzable T_3I^{131} component was observed. This suggests a remarkable competition between filter paper and protein for the T_4 hormone.

Quantitative studies using thyroxine and significantly influenced by glass and filter paper contact. The monitored dis-equilibrated flow dialysis system is well suited to quantitate the significance of these factors.

T 11. *Sulfur-35 Therapy of Mycosis Fungoides.* **R. R. Lund and R. G. Davis (U.S. Naval Hospital, Bethesda)**

The intense and often intractable pruritis associated with cutaneous lymphoma may not show satisfactory response to conventional therapy. In patients who have shown a good response to multiple doses of superficial X-ray therapy, repetition of such treatment may be limited by the skin tolerance. For such patients, an additional form of radiation therapy is desirable.

Sulfur-35 was chosen as such an agent because of the long established empirical use of sulfur in dermatology and the known ability of the skin to concentrate S^{35}. The weak beta radiation of S^{35} would contribute a low radiation dosage to tissues not concentrating the sulfur.

Two patients with mycosis fungoides and severe pruritis have been treated with S^{35} as dilute H_2SO_4, administered orally in doses varying from 10 mc to 30 mc. One patient exhibited a total remission of signs and symptoms for six months following the first dose of 10 mc. Pruritis was gone within four days and objective improvement in skin lesions was noted within two weeks. Subsequent remissions of nine and two and a half months were produced with doses of 30 mc and 20 mc, respectively.

The second patient received no observable benefit from the first dose of 30 mc. A second dose of 30 mc administered two months later resulted in exacerbation of the pruritis for three to four days with subsequent remission of pruritis and diminution in cutaneous lesions for three months.

Studies of urinary and stool excretion, of blood levels, and cutaneous distribution of S^{35} are underway. Although the initial results suggest only palliative benefit from this therapy, the marked relief afforded these patients justifies further study.

T 12. *The Uses of Kr-85.* **R. J. Sanders (V. A. Hospital and University of Colorado School of Medicine, Denver)**

$Krypton^{85}$, a beta emitting isotope of an inert gas, has many of the desired properties of circulation indicators. It can be inhaled or it can be dissolved in water and injected intravenously, or intra-arterially. It is poorly soluble in fluid (air:fluid partition coefficient is 20:1) so that when it is injected, it is rapidly exhaled. More than 95% of the gas is excreted on

its first circulation through the lungs. This is one of the chief advantages of Kr^{85} over other indicators: its rapid excretion so that the recirculation is minimal. This permits Kr^{85} to be used repeatedly or even continuously without appreciably raising the radioactive background in the blood.

Krypton^{85} was first used in patients as a substitute for N_2O, by the inhalation route. Measurements of cerebral blood flow and coronary blood flow have been made with Kr^{85} inhalation, as well as the detection of left-to-right cardiac shunts.

Although poorly soluble in fluid, it is possible to dissolve enough Kr^{85} in saline to prepare a useful indicator. Following its intravenous injection measurements of cardiac output, arm-to-lung circulation time, pulmonary function, and right-to-left cardiac and pulmonary shunts can be made.

Following intra-arterial injection, regional and organ blood flow can be determined by continuously recording the changes in concentration of exhaled air. Other areas where Kr^{85} has been used as an indicator is to evaluate portacaval and portapulmonary anastomoses.

Because of its unique properties, Kr^{85} is proving itself to be a most versatile indicator.

T 13. *Preparation of Hospitals for the Reception and Management of Industrial Radiation Casualties.* ALBERT A. SPRITZER, RAYMOND MOORE and NIEL WALD (Department of Occupational Health, University of Pittsburgh, Pittsburgh)

The continuing increase in the number of individuals whose occupation bears the potential to produce accidental radiation contamination and injury requires that adequate preparations be made for their optimal medical management. Experience gained in the preparation of three hospitals for the reception and care of industrial radiation casualties is reviewed.

Objectives of a hospital radiation casualty plan are compared and contrasted with those of civil defense planning. The nature of hospital organization, the training of hospital personnel and the means for overcoming certain hospital deficiencies for his purpose are considered. The basic elements of an industrial plant disaster plans are described in order to demonstrate a practical approach toward its extension to fit the hospital radiation casualty plan. Potential patients are divided into three categories; i.e., those externally irradiated, those externally contaminated, and those containing an excessive internal body-burden of radioactive nuclides. The clinical management of the associated problems is discussed.

T 14. *Dilution Studies of K-42 Na-22 and Tritium in Familial Periodic Paralysis.* PETER J. TALSO and MICHAEL F. GLYNN (Stritch School of Medicine, Loyola University and Cook County Hospital, Chicago)

Periodic Paralysis represents a rare clinical entity which has been recognized for the past eighty years. Several studies have served to delineate the mechanisms which induce the episodes of paralysis. Despite this fact, studies of whole body composition in this disease have been limited. Recently, five cases of familial periodic paralysis were brought to our attention simultaneously. Intensive studies with electromyograms, electrocardiograms, serum and tissue electrolytes have confirmed the diagnoses. In all patients during the non-paralytic state, total body water was measured with tritium, exchangeable sodium with Na_{22} and exchangeable potassium with K_{42}. The values for total body water were within normal limits, the mean value for Na_E was 67.1 mEq./Kg. (normal = 37.8 mEq./Kg.), and the mean value for K_E was 38.6 mEq./Kg. (normal = 47.4 mEq./Kg.). All patients have been treated with a new aldosterone antagonist 2, 4, 7-Triamino-6-phenyl pteridine in a dose of 200 mgm. On this regimen, all patients have become asymptomatic and have required no potassium supplements. The effects of this therapy on the measured parameters of body composition will be described.

T 15. ***Major Arterial Visualization Utilizing Right Atrial Injection and RISA Circulation Time.*** **Carl L. Williams, Timothy Takaro, and Stewart M. Scott (Veterans Administration Hospital, Oteen, North Carolina)**

Angiographic information concerning renal arterial involvement and the status of the peripheral outflow obtained prior to operation for abdominal aortic aneurysm may be extremely useful for the surgeon. At times, the diagnosis of abdominal aneurysm may be in doubt, and in these instances also angiography may be of great value. The safest, simplest, and most satisfactory method for obtaining this information is by intravenous angiography.

The purpose of this study was to evaluate factors in intravenous angiography which would increase the percentage of successful studies and which might improve the detail and contrast obtained. By combining the technique of right atrial dye injection as used by Zerbi-Ortiz and Weldon with accurate circulation timing as recommended by Bernstein et al, it was thought that these aims might be accomplished.

To date, 55 patients, being studied primarily for aortic aneurysms, have been examined by the above technique. Thirty of these patients had circulation times determined with decholin and 25 have had the determination using RISA. Ten patients had circulation timing with both methods.

The conclusions suggested by our studies to date include:

(a) Circulation times are most accurately determined with RISA and this method has a wider range of applicability because it does not require a cooperative patient. Thus, psychotic patients, the extremely elderly, and the anesthetized patient may all be readily examined.

(b) Timing with isotopes is most accurate when the scintillation counter is situated proximal to the aneurysm rather than directly over it.

(c) With the above described technique, manually operated long cassette changers may be utilized enabling one to simultaneously evaluate outflow as well as the area of primary pathology.

(d) Measurement of cardiac function by electrocardiogram and right atrial pressures through a second catheter confirms the safety of high pressure right atrial dye injection.

T 16. ***Technical Problems from Employment of Erythrocytes As the Receptors in the Measurement of Unsaturated Thyroid-binding Globulin.*** **George E. Thoma, Walter DiGiulio, and Paul Weinhold (Section of Nuclear Medicine, Department of Internal Medicine, St. Louis University School of Medicine, St. Louis)**

The principal technical factors that affect the erythrocyte uptake of triiodothyronine (T3) are errors that can be attributed directly to the use of the erythrocyte as the competitive receptor for T3.

First, the phenomenon of erythrocyte binding of triiodothyronine is one of surface adsorption (Crispell), therefore any qualitative changes in the erythrocytes will affect the strength of binding by this receptor. Furthermore, variations in the mass of this receptor are unavoidable and the hematocrit is at best only a gross estimation of the magnitude of this mass. Since this test measures one of the end products of an equilibrium reaction that follows the law of mass action, this variability in the mass of one component assumes some significance. It has also been shown that qualitative alterations in the erythrocytes due to disease states such as polycythemia will alter the uptake.

Second, the per cent uptake of T3 by the erythrocytes is a function of the number and the vigor of the washings. Meade showed that the removal of T3 from the erythrocytes followed a first order reaction curve and that after sufficient washing virtually all of the T3 would be eliminated from the surface of the cells. Though duplicate samples may agree closely because they have been subjected to equal washings, there is no guarantee that the vigor of washing is not varying from day to day. This is especially true in those situations where the test is performed only sporadically.

We found that by measuring plasma uptake rather than erythrocyte uptake, we could eliminate washing of red cells with some improvement in the reproducibility of the test. This modification, however, still does not eliminate qualitative and quantitative variations in the erythrocytes. Therefore, we have further modified the test by using resins as receptors of triiodothyronine.

T 17. ***The Compound Positron Detector—A Feasibility Study.*** **W. Paul (Department of Pathological Chemistry, University of Toronto, Toronto)**

This project is to investigate the potential advantage of using a coincidence paired array of scintillation detectors for the measurement of the distribution of a positron emitter in the human body. The effort is based on the application to the brain where considerable information has been obtained using Arsenic-74 as the positron emitter. In order to be useful the resolution of the paired detectors must be small, preferably no larger than 2 cms. in diameter. The recent availability of ten dynode three-quarter inch diameter photomultipliers suggests that an array with adequate, though not good, resolution might bear investigation. Earlier experiments by Bender indicated that the six dynode photomultiplier was not suitable, but experiments with the ten dynode phototube appear to be unreported.

Preliminary experiments using single pairs of photomultipliers indicate good pulse resolution of the 0.51 Mev. annihilation gamma photon and a potential advantage over the collimated large crystal scanning system.

Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the July, 1962 issue must be in the hands of the Editor before June 1, 1962.

Technical Exhibits

ABBOTT LABORATORIES
North Chicago, Illinois

ATOMIUM CORPORATION
Waltham, Massachusetts

BAIRD-ATOMIC, INC.
Cambridge, Massachusetts

COULTER ELECTRONICS, INC.
Hialeah, Florida

CURTIS NUCLEAR CORPORATION
Gardena, California

ENCYCLOPAEDIA BRITANNICA, INC.
Chicago, Illinois

GREAT BOOKS OF THE WESTERN WORLD
Chicago, Illinois

ISO-SERVE, INC.
Cambridge, Massachusetts

LANDSVERK ELECTROMETER COMPANY
Glendale, California

NUCLEAR-CHICAGO CORPORATION
Des Plaines, Illinois

NUCLEAR CONSULTANTS CORPORATION
St. Louis, Missouri

NUCLEAR INDUSTRIES, INC.
Valley Stream, New York

NUCLEAR SCIENCE & ENGINEERING CORP.
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OAK RIDGE NATIONAL LABS.
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PICKER X-RAY CORPORATION
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RADIATION COUNTER LABS., INC.
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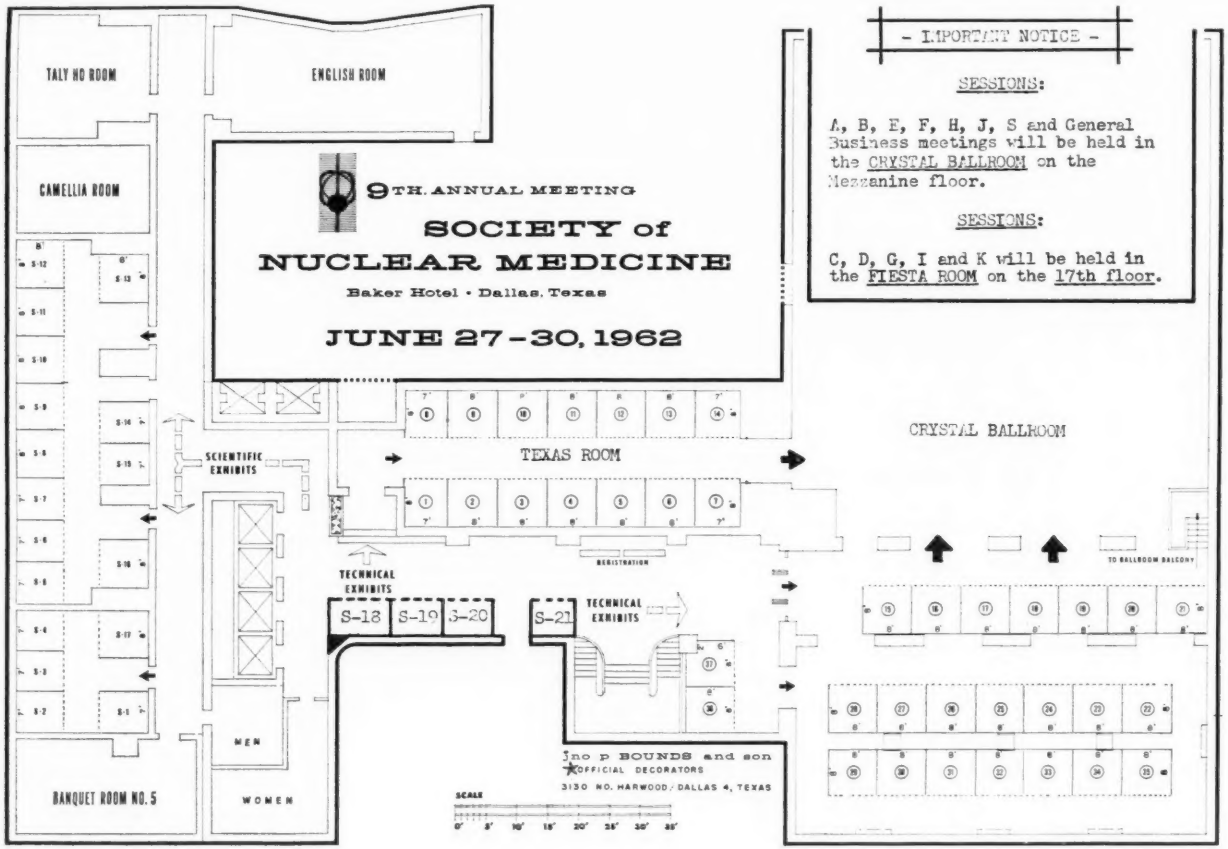
SCIENTIFIC PRODUCTS
Evanston, Illinois

E. R. SQUIBB & SONS
New York, New York

TRACERLABS, INCORPORATED
Waltham, Massachusetts

VOLK RADIOCHEMICAL COMPANY
Skokie, Illinois

WESTRONICS, INC.
Fort Worth, Texas


TALY HO ROOM
ENGLISH ROOM
CAMELLIA ROOM
9TH. ANNUAL MEETING
SOCIETY of
NUCLEAR MEDICINE
Baker Hotel • Dallas, Texas
JUNE 27-30, 1962
- IMPORTANT NOTICE -
SESSIONS:
A, B, E, F, H, J, S and General Business meetings will be held in the CRYSTAL BALLROOM on the Mezzanine floor.
SESSIONS:
C, D, G, I and K will be held in the FIESTA ROOM on the 17th floor.
CRYSTAL BALLROOM
TEXAS ROOM
SCIENTIFIC EXHIBITS
TECHNICAL EXHIBITS
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TECHNICAL EXHIBITS
REGISTRATION
TO BALLROOM BALCONY
MEN
WOMEN
BANQUET ROOM NO. 5
Jno P BOUNDS and son
OFFICIAL DECORATORS
3130 NO. HARWOOD, DALLAS 4, TEXAS
SCALE

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Attend the 9th Annual Meeting

of the

Society of Nuclear Medicine

BAKER HOTEL—DALLAS, TEXAS

June 27-30, 1962

9th Annual Meeting

Thursday evening, June 28, 1962

SOCIAL HOUR AND ANNUAL BANQUET —FIESTA ROOM AND TERRACE ROOM (17th floor)

6:45- 7:45 Social Hour—Cocktails (cash bar) —FIESTA ROOM
8:00- 9:30 Annual Banquet—Dress, Optional —TERRACE ROOM
9:30-12:00 Dancing —TERRACE ROOM
9:30-12:00 Smoker and Shop Talk —FIESTA ROOM

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LADIES PROGRAM
9th Annual Meeting

Wednesday, June 27, 1962

9:00 A.M. Registration—MEZZANINE—Baker Hotel

9:00 A.M. Ladies Hospitality Room—CAMELIA ROOM.
The Camelia Room will be available as the Ladies Hospitality Room from 9:00 A.M. to 5:00 P.M. each day throughout the meeting. This will provide an opportunity to meet your friends and to rest.

Scientific Sessions will begin at 3:00 P.M. and will continue until 5:00 P.M. They will resume at 8:00 P.M. and end at approximately 10:30 P.M. Wednesday evening will provide an excellent opportunity for viewing one or two excellent stage productions in Dallas. Complete details will be available in the Ninth Annual Meeting Announcement.

Thursday, June 28, 1962

10:30 A.M. Coffee Break.

1:30 P.M. Non-technical discussion of nuclear medicine. A special scientific program has been prepared for the wives of the Society's members. This program has been designed to provide interesting aspects in a non-technical and layman's language.

6:45 P.M. Social hour preceding Annual Banquet.

8:00 P.M. Annual Banquet (Dress optional).

9:30 P.M. Dancing.

Friday, June 29, 1962

A tour of Dallas including the Dallas Health and Science Museum, interesting homes and gardens in Dallas and Brunch at the Brookhollow Golf Country Club. Cost including brunch: $6.75 per person.

6:00 P.M. The Society has no planned activity for Friday evening which would present an opportunity to visit Six Flags Over Texas (A Texas Disneyland). Complete details will be available at the registration desk at the meeting.

Saturday, June 30, 1962

9:00 A.M. Scientific Sessions will begin at 9:00 A.M. and end at 12:00 noon. This morning has been left open for shopping, sight-seeing and resting.

3:00 P.M. Ranch Party for the entire family. This will include boating, pony rides, fishing, swimming, square dancing and a Chuck Wagon Dinner at 6:00 P.M. Complete details appear on the mailing distributed to the entire membership.

Sunday, July 1, 1962

Planned tours to Mexico City and other interesting places in Mexico arranged by the Del Prado Travel Bureau. Tour selections have been mailed to the entire membership.

We earnestly urge that you make advance reservations for the various activities indicated above in order that you will not be disappointed in the event the supply of tickets become exhausted.

—Ladies General Arrangements Committee

THE PRESIDENT'S ANNUAL REPORT

In behalf of the officers and members of the Society, all scientists interested in any phase of nuclear medicine are cordially invited to attend our Ninth Annual Meeting in Dallas, Texas. Many interesting and current problems will be presented and discussed.

In the Federal Register of January 1962 the A.E.C. published proposed amendments in the licensing and regulations of the medical users of isotopes. These changes are briefly as follows:

1. 10CFR 30:11. Any licensed physician possessing an adequate radiation survey instrument may receive up to 200 μc of Cr^{51} and in capsules or prepackaged forms I-131 up to 200 μc, Co^{58} and Co^{60} to 10 μc.

2. 10 CFR 30.26. He may use I-131 up to 15 mc. and P-32 to 10 mc.

The changes are designed to permit any licensed physician to use the above isotopes with no attempt to outline his qualifications. The Southeastern chapter and the Southwestern chapter have gone on record opposing these alterations. It is their belief as well as many, but not all members of the Society that these amendments do not provide adequate safeguards in the clinical use of radioactive material. Because of the dissenting opinion, the division of Regulation and Licensing of the A.E.C. was requested to postpone action on these amendments until they could be presented to the Society as a whole at the Dallas meeting.

In formulating an opinion as to what sort of qualifications, if any, are necessary to use isotopes in the medical fields it might be well to correlate this to an opinion as to what sort of qualifications if any, are necessary to become a member of the Society of Nuclear Medicine. The two are closely related.

The Journal of Nuclear Medicine was born under rather difficult circumstances, it has been nursed along by the editor, George Thoma, and the publisher, Sam Turiel, into a good-sized thriving adolescent. The papers are being processed more rapidly, the Journal is now being published on time, and not the least important, it is operating in the black. It bids fair to become a vigorous, self-sufficient adult.

The Dallas meeting has every prospect of being bigger and better than even the last one. The Society has grown to approximately 1700 members, the field it embraces has grown prodigiously, the papers—about 90 in all—represent the best scientific and clinical research in the area. Dr. Glenn T. Seaborg will speak at the banquet. Dallas is a sprightly Texas city, and Texans are entertaining, charming hosts.

It has been a sincere pleasure serving as your President. I express heartfelt thanks to the members of the Executive Committee, the Board of Trustees and the Chairman of the various Committees for their efforts and loyal support.

Lindon Seed, M.D.
President.

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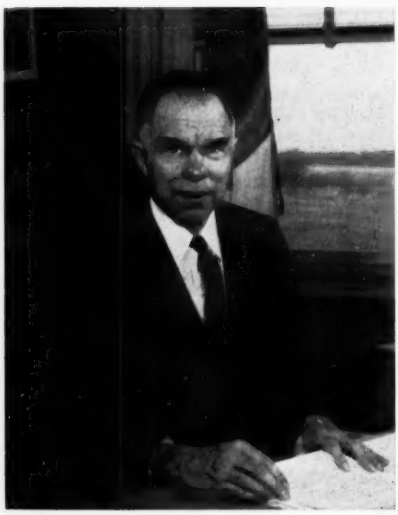
Glenn Theodore Seaborg



Dr. Glenn T. Seaborg[1] was born in Ishpeming, Michigan, on April 19, 1912, a son of H. Theodore and Selma Erickson Seaborg. At the age of ten he moved with his family to Home Gardens, California, now a part of South Gate, near Los Angeles. From 1925 to 1929 he attended David Starr Jordan High School in Los Angeles, graduating in 1929 as valedictorian of his class. It was in high school that Dr. Seaborg's interest in chemistry and physics was kindled by his science teacher, the late Dwight Logan Reid.

Dr. Seaborg entered the University of California at Los Angeles in 1929. He was elected to Phi Beta Kappa, national honorary scholastic fraternity, in his junior year and received a bachelor of arts degree in chemistry from the University in 1934. In 1934 he entered the University of California at Berkeley where he received the degree of doctor of philosophy in chemistry in 1937. From 1937 to 1939, Dr. Seaborg was a research associate in chemistry on the Berkeley campus, working as the personal laboratory assistant of the late Dr. Gilbert Newton Lewis, then Dean of the College of Chemistry, with whom he published a number of scientific papers.

In 1939, Dr. Seaborg was appointed an instructor in chemistry at the University of California, Berkeley. In this post, he became co-discoverer, in 1940, of element 94 (plutonium), the first of a number of transuranium elements which he was to help discover during the next 18 years. He was promoted to assistant professor of chemistry at the University in 1941 and in that year became co-discoverer of the nuclear energy isotope, plutonium 239. Also, in 1941, he helped to discover the uranium isotope U-233. In 1942, he was also co-discoverer at the University of the long-lived isotope of neptunium (element 93) and of the existence in nature of plutonium in extremely small concentrations.

In April, 1942, Dr. Seaborg was given a leave of absence from the University of California to head the plutonium work of the Manhattan Project at the University of Chicago Metallurgical Laboratory. He remained at the laboratory until May, 1946, as chief of the section working on transuranium elements. One of his principal responsibilities there was directing the development of the chemical process which was used for the separation of plutonium from fuel elements irra-

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[1]Dr. Seaborg will present the Third Annual Lecture–Nuclear Pioneer Series at the 9th Annual Meeting, Society of Nuclear Medicine, Dallas, Texas, June 28, 1962.

diated in the production reactors at the Hanford installation at Richland, Washington. While at the laboratory, Dr. Seaborg, with his associates, also discovered two more transuranium elements, element 95 (americium) and element 96 (curium), both in 1944.

In 1945, although still on leave from the University of California, Dr. Seaborg was promoted from assistant to full professor of chemistry at the University's Berkeley campus. In May, 1946, he returned to the Department of Chemistry at the University and also took responsibility for direction of nuclear chemical research at the Lawrence Radiation Laboratory, operated for the Atomic Energy Commission by the University. In 1954 he was named Associate Director of the Laboratory, a position which he resigned upon coming to the Commission.

In postwar research, Dr. Seaborg and his colleagues at the University discovered element 97 (berkelium) in 1949 and element 98 (californium) in 1950. In 1952, working with University scientists and scientists of the AEC's Argonne National Laboratory and of the Los Alamos Scientific Laboratory, he discovered element 99 (einsteinium) and, in 1953, element 100 (fermium). He was co-discoverer of element 101 (mendelevium) in 1955 and element 102 in 1958 at the University of California.

In addition to the discovery of transuranium element, Dr. Seaborg and his colleagues are responsible for the identification of more than 100 isotopes of elements throughout the periodic table. He also is author of the actinide concept of heavy element electronic structure. In this connection, Dr. Seaborg demonstrated that the heavy elements form a "transition" series of actinide elements in a manner analagous to the rare earth series of lanthanide elements. The concept demonstrated how the heavy elements fit into the periodic table and thus demonstrated their relationships to the other elements.

The body of information assembled in Dr. Seaborg's laboratory has made it possible to predict the radioactive characteristics of many isotopes of elements still to be found. Under Dr. Seaborg's leadership, also, whole new bodies of methodology and instrumentation have been developed and have become a cornerstone of modern nuclear chemistry. Dr. Seaborg is the author of approximately 200 scientific papers, including a number of comprehensive reviews and compilations in scientific publications. He is also author and co-author of several books on chemistry and the elements.

Dr. Seaborg was appointed by President Truman in 1946 to be a member of the Atomic Energy Commission's first General Advisory Committee, a post he held until 1950. He was a member of the Joint Commission on Radioactivity of the International Council of Scientific Unions from 1946 to 1956; of the Committee on Standards and Units of Radioactivity of the National Research Council from 1947 to 1951, and of the President's Science Advisory Committee from 1959 to 1961.

Among other honors Dr. Seaborg was named, in 1947, as one of America's 10 outstanding young men by the U. S. Junior Chamber of Commerce and in the same year was made recipient of the American Chemical Society's Award in Pure Chemistry. He was awarded the John Ericsson Gold Medal by the American Society of Swedish Engineers in 1948 and the Nichols Medal of the New York Section of the American Chemical Society, also in 1948. With Prof. E. M. McMillan,

of the University of California, he was awarded the Nobel Prize in Chemistry in 1951. He won the John Scott Award and Medal of the City of Philadelphia in 1953 and the Perkin Medal of the American Section of the Society of Chemical Industry in 1957. Dr. Seaborg was named recipient in November, 1959, of the Atomic Energy Commission's Enrico Fermi Award for his outsanding work in the field of nuclear chemistry and for his leadership in scientific and educational affairs.

Dr. Seaborg is an Honorary Fellow of the Chemical Society of London and of the Royal Society of Edinburgh. He is a Fellow of the American Institute of Chemists, the New York Academy of Sciences, the California Academy of Sciences, the American Physical Society and the American Association for the Advancement of Science. He is also a member of the American Chemical Society, the American Nuclear Society, the American Academy of Arts and Sciences, the American Philosophical Society, the Royal Swedish Academy of Engineering Science, the Royal Society of Arts (England) and the American Scandinavian Foundation.

Honorary degrees awarded to Dr. Seaborg include doctor of science degrees from the University of Denver, 1951; Gustavus Adolphus College, 1954; Northwestern University, 1954; University of Notre Dame, 1961; Ohio State University, 1961; Florida State University, 1961; University of Maryland, 1961; and Temple University, 1962: and the degree of doctor of laws from the University of Michigan in 1958. In addition to his membership in Phi Beta Kappa, Dr. Seaborg also is a member of Sigma Xi, Pi Mu Epsilon, Alpha Chi Sigma and Phi Lambda Upsilon fraternities.

Dr. Seaborg was a member of the Board of Directors, Nuclear Science and Engineering Corp., Pittsburgh, and a consultant for the U. S. Rubber Co. and Bell Telephone Laboratories. He is a member of the advisory board of the Journal of Inorganic and Nuclear Chemistry, a former member of the advisory board of Chemical and Engineering News and a former member of the editorial board of the Journal of the American Chemical Society.

In August, 1958, Dr. Seaborg was appointed Chancellor of the University of California at Berkeley. He served in that capacity until his appointment to the Atomic Energy Commission. He is currently considered by the University of California to be on leave from his post as Professor of Chemistry.

Dr. Seaborg was nominated to the Commission by President Kennedy on January 21, 1961 and was confirmed by the United States Senate on February 24, 1961. He was designated Chairman of the Atomic Energy Commission by the President on March 1, 1961, which is also the date he took the oath of office. He succeeded former Chairman John A. McCone who resigned as of January 20, 1961. Dr. Seaborg's term of office expires on June 30, 1963.

On June 6, 1942, Dr. Seaborg married the former Helen L. Griggs, then secretary to the late Dr. Ernest O. Lawrence. The Seaborgs have six children: Peter, Lynne, David, Stephen, John Eric and Dianne.

Dr. Seaborg's chief hobby is golf. His favorite spectator sport is football, although he follows baseball with interest. From 1953 to 1958 he served as the University of California (Berkeley) Faculty Athletic Representative.

JOURNAL OF NUCLEAR MEDICINE 3:249, 1962

Preliminary Progress Note[4]

The Synthesis of Co^{57} Tetraphenylporphinesulfonate and Its Use in the Scintillation Scanning of Neoplasms

James Winkelman, M. D.[1] John G. McAfee, M. D.[2] Henry N. Wagner, Jr., M. D.[2] R. Gordon Long, M. D.[3]

Baltimore, Maryland

INTRODUCTION

Tumors may be visualized by scintillation scanning if gamma-emitting compounds can be found which concentrate to a high degree in neoplastic tissues. The compound alpha, beta, gamma, delta tetraphenylporphinesulfonate (TPPS) accumulates in the Walker 256 carcinosarcoma to a greater extent than in any other tissue of the tumor-bearing rat (7). In an effort to determine whether TPPS could be used as a vehicle to deliver a gamma-emitting radionuclide to tumors, we have synthesized the cobalt (Co^{57}) chelate of TPPS and evaluated the distribution of the Co^{57} after injection into ependymoma-bearing mice.

METHODS

Tetraphenylporphine (TPP) was prepared from pyrrole and benzaldehyde by the method of Rothemund and Menotti (4), and sulfonated by reaction wth concentrated sulfuric acid. The chelation of Co^{57}* was accomplished by refluxing the TPPS and $Co^{57}Cl_2$ at a molar ratio of 100:1, for 15 minutes in dilute acetic acid. Free Co^{57} was elupted from an alumina column (aluinum oxide, basic, anionotropic, obtained from Woelm) with water. The Co^{57} chelate of TPPS was eluted with dilute ammonium hydroxide. The material was then concentrated and freed of ammonia by evaporating to dryness on a hot plate. After redissolving in 0.1 N sodium chloride solution, the labeled TPPS was sterilized by autoclaving.

The Co^{57} labeled compound was then injected in 10 microcurie amounts into the tail vein of inbred C-57 strain black mice (Jackson Memorial Laboratory,

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[3]Department of Neurological Surgery, The Johns Hopkins Hospital, Baltimore, Maryland.
[4]Preliminary Progress Note: See page 233.
*Obtained as cobaltous chloride, $Co^{57}Cl_2$, in 0.5 M HCl, from Nuclear Science and Engineering Corporation, Pittsburgh, Pennsylvania.

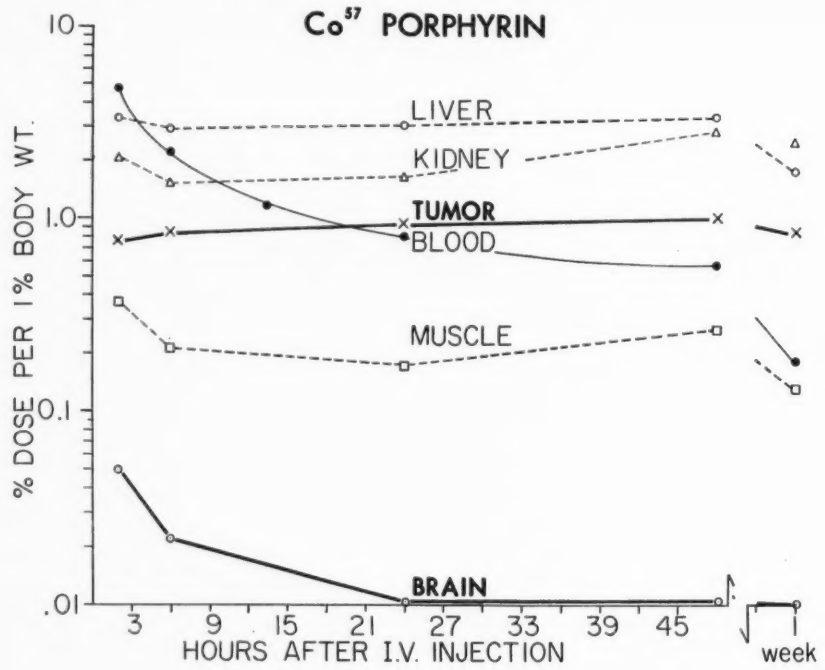

Fig. 1

Bar Harbor, Maine) bearing four week old transplanted tumors. Histologically, these subcutaneous tumors were ependymomas, and were orignally produced by intracerebral implantation of methylcholanthrene crystals (3). This experimental tumor was used previously in studies of the distribution of radionuclides, since the tumor:brain concentration ratios in the mouse correlate well with those obtained in human gliomas (2).

Groups of mice were sacrificed from three hours to seven days after injection. To facilitate removal of blood from the tissues by saline perfusion, the mice were given heparin intraperitoneally 10 minutes before sacrifice. Weighed samples of tumor, blood, brain, liver, kidney, muscle, and other organs were dissolved in concentrated nitric acid, and their concentration of radioactivity was determined in a well-type scintillation detector.

In addition, the distribution of the labeled TPPS was measured in four Sprague-Dawley rats bearing 12 day old Walker 256 carcinosarcoma.

RESULTS

The distribution of radioactivity in 39 tumor-bearing mice is shown in Figure 1. The concentration of radioactivity is expressed as the per cent of administered dose per one per cent body weight. The tumor to brain concentration ratio is approximately 60:1. This is higher than that of any other labeled compound

which has been used for brain tumor localization in man (3), including I-131 albumin and Hg-203 Neohydrin. This high concentration gradient was attained after 24 hours and persisted for at least one week. The absolute concentration of radioactivity in the tumor was approximately one per cent of the administered dose per one per cent body weight. The concentration in tumor fell only slightly during the first week, while the blood concentration fell continuously. High levels of radioactivity were found in the liver, the principal site of porphyrin catabolism, and in the kidney, the principal site of porphyrin excretion. The concentration of radioactivity was low in thymus, colon, stomach, and other organs not represented in Figure 1.

By total body counting a series of six white mice over an eight week interval, the biological excretion of Co^{57} TPPS was determined. The initial effective half-life was eight days followed by a slower component of 28 days.

The concentration of radioactivity in the rat tissues, as well as in the Walker 256 carcinosarcoma, was similar to that of the ependymoma-bearing mice. The tumor, growing subcutaneously in the flank of the rat, could be delineated by scintillation scanning (Fig. 2). Concentration of the radioactivity could be seen in the liver as well as the tumor.

DISCUSSION

The physical characteristics of the radionuclide Co^{57} are well suited to scintillation scanning. Its gamma emissions of .014 and .130 mev are insignificant, so that it may be regarded as monoenergetic. Its principal gamma emission of .123 mev is readily collimated, resulting in good resolution; yet its energy is sufficiently high to permit the demonstration of lesions at depths of 8 to 10 cms within the body. Its half value layer in water is approximately 4.3 cms compared with 2.2 cms for I-125, and 6.2 cms for I-131. The complete absence of beta emission, and the low I-gamma (0.55 r per mc-hr at 1 cm) result in reduced radiation dosages, compared with other radionuclides commonly used in medicine. Cobaltous ions, which may be released metabolically from labeled substances are not utilized by the body, but are promptly excreted. The long physical half-life of Co^{57} of 270 days results in a long "shelf-life" for labeled compounds.

TPPS is a very suitable "carrier" for radiocobalt for tumor-localization studies. It is not chemically toxic at the levels used in animal studies (7). The chelation of cobalt in other TPP derivatives is extremely stable, even in acidic solutions, and may be sterilized by heat. It is much more stable than Cr^{51} porphyrins which have been used in the past. Because of the longer physical half-life, it is more practical for diagnostic studies than Cu^{64} labeled porphyrins (2). It is possible that some cobaltous ions may be released metabolically. TPPS is a purely synthetic compound: hence, the variability, difficulties of separation, and impurities of biological products such as hematoporphyrin or protoporphyrin are completely avoided.

Despite the relatively long effective half-life of Co^{57} TPPS, the calculated radiation dosage to humans is well within permissible levels, assuming that the tissue distribution in man is similar to that of the mouse. In comparison with

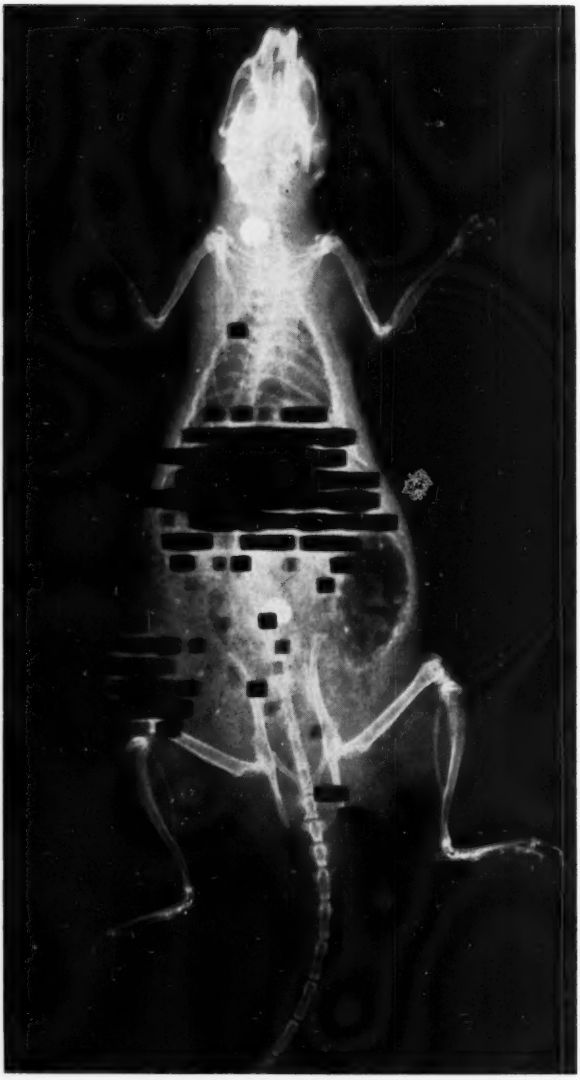

Fig. 2

similar activities of I-131 labeled serum albumin, the total body radiation dosage would be somewhat less, and the dosage to the blood considerably less. The organ with the highest concentration—the liver—would not receive much more than the total body dose, because of the absence of beta emissions.

Like other labeled substances which produce good tumor to brain concentration ratios, Co^{57} TPPS is portein-bound in the blood. It migrates with the serum proteins during electrophoresis (7). Approximately 95 per cent of the compound

is in the plasma fraction and the remaining five per cent in the red cell fraction of whole blood. About 95 per cent of the plasma fraction is precipitated with trichloroacetic acid and 92 per cent with phosphotungstic acid.

The mechanism of localization of this compound in tumor tissue is not known. It is possibly one of simple diffusion. Previously, it has been postulated that porphyrins merely become trapped in the necrotic debris of tumors by protein binding (2). However, the presence of administered hematoporphyrin has been clearly demonstrated in the cytoplasm of intact tumor cells by fluorescence microscopy (6). The hematoporphyrin is firmly bound to protein of the soluble fraction of cytoplasm.

Comparison of the Co^{57} labeled tetraphenylporphinesulfonate with other substances that have been used for the delineation of brain tumors will be presented in detail elsewhere (3). The results to date suggest the concentration of the material in experimental tumors is sufficiently high to warrant evaluation of its usefulness in scintillation scanning of human brain tumors and other neoplasms.

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Announcement

A symposium "Advances in Radioisotope Scanning" will be given at the Medical Division of the Oak Ridge Institute of Nuclear Studies, October 22-26, 1962. Lectures will be given by invited experts from various institutions. Enrollment is limited to 40 participants. Applications are available from Ralph M. Kniseley, M.D., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.

INFORMATION FOR AUTHORS

The Journal of Nuclear Medicine will publish original articles in clinical medicine, basic and clinical medical research, physics and chemistry dealing with the use of isotopes in humans, and articles on related subjects. The latter includes dosimetry, instrumentation, protection, techniques and biologic effects contributing to the use or effects of isotopes in clinical medicine or the clinical effects of ionizing radiation. Articles are accepted for publication on the condition that they are contributed exclusively to this journal.

MANUSCRIPTS must be typed doubled or triple spaced, the latter being preferable, and with at least a one-inch margin on each side of a standard size page. The original with one carbon copy must be provided.

TABLES must have captions and be numbered consecutively in Arabic numbers.

ILLUSTRATIONS should be in black ink on hard white paper with all lettering of sufficient size and clarity to permit reduction. Each illustration must be identified by a label pasted to the back indicating its number, the author's name and an abbreviated title of the article. The top of the illustration must be clearly indicated. Illustrations must have descriptive legends grouped on a separate sheet (double spaced).

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Unused manuscripts will be returned by regular mail. Used manuscripts are not returned, however, used illustrations are returned after the article is published.

JOURNAL OF NUCLEAR MEDICINE 3:255, 1962

"Blind End" Technique for Iridium[192] Removable Nylon Ribbon Interstitial Implants:[1] Applicable to Carcinoma of Rectum and Vagina.

Leonard M. Liegner, M.D.[2]

New York City

INTRODUCTION

Post-operative recurrent cancer deeply situated in the true pelvis and extending into the perineum is generally inaccessible to interstitial Radium or Radioisotope implantation. Local vault or vaginal mucosal nodules have been approached with intravaginal cone or infrequently by limited Radium needle implantation. More extensive superficial vaginal mucosal involvement may lend itself to intravaginal radium line source therapy. Vulval or anal cancers, primary or recurrent, have likewise been implanted as localized accessible tumors.

The problems of recurrent cervix or corpus cancer centrally located have been acceptably handled with further excisional surgery or by external and/or intravaginal irradiation. In other instances, if at the time of operation the recurrent disease is too extensive for resection permanent implants[1,2] of Iridium[192] seeds can be used at the time of open surgery.

In our experience recurrent disease following abdominal-perineal resection for carcinoma of the rectum manifests itself as an extensive cylinder of tumor usually midline which may invade the perineal skin and perineum and in the female also involving the vaginal tract. Furthermore, direct cephalad extension is also seen to the hollow of the sacrum or promontory. Reoperation for further exenteration in an already exenterated field rarely tempts even the most aggressive surgeon. Just as most surgeons will hesitate to explore in the face of a seemingly unresectable situation, the radiation therapist likewise approaches such extensive disease with trepidation knowing full well the difficulty of planning treatment for a single block of pelvic-perineal tumor. Disease of this extent would require either large field rotational therapy which is undesirable or parallel

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Presented at Eighth Annual Meeting, Society of Nuclear Medicine, Pittsburgh, Penn. June 14-17, 1961.

opposing pelvic fields combined with direct perineal fields. Since the perineum is inordinately prone to intense reaction even with supervoltage irradiation, such combined pelvic-perineal planning is not inviting. To cope with extensive recurrent cancer in the pelvic-perineal region I have developed the "Blind End" Iridium^{192} Removable Nylon Ribbon Interstitial Implantation Technique.

1. *The Iridium^{192} Nylon Ribbon Kit–*

The basis of the technique is the ingenious development by Dr. Ulrich Henschke, of Memorial Center, of the Iridium^{192} Nylon ribbon kit[1], and his suggestion to me that inaccessible tumors could be implanted with nylon ribbons. Each kit can be loaded to contain up to 28 nylon ribbons, 1 meter long, each loaded with 12 Ir^{192} sources, spaced 1 cm apart and held in their position without spacers by the elasticity of the nylon ribbon. The cylindrical Ir^{192} sources are 3 mm long and 0.5 mm in diameter. They consist of an Iridium cylinder which is sheathed with 0.2 mm of stainless steel for the absorption of beta particles of the Ir^{192} which have a maximum energy of 0.67 Mev. The eleven (11) gamma lines of Ir^{192} range from 0.136 Mev to 0.613 Mev with 94 per cent of all gamma energy emitted at the 0.296, 0.308, 0.316 and 0.468 Mev level.

The implantation needles are made from standard 17 gauge hypodermic needle tubing and are supplied in the kit in 20 cm length without stylet. For the purpose of the "Blind End" technique herein described, Dr. Ulrich Henschke kindly supplied us with stainless steel tube stylets shorter than the implantation needles. Furthermore, since the technique involved deep implantation he provided me with 30 cm long implantation needles with appropriate stylets. Experience with the technique led us to the modification of the implantation needle head whereby we machined off a 0.5 cm long hemi-cylinder of the needle head to facilitate threading of the nylon ribbons. Uni-construction button-clips are also supplied with the kit which serve for anchoring the nylon ribbons to the skin.

Figure 1, shows the stainless steel enclosed lead container used for shipping, storing and disposal of nylon ribbons. The container is supplied in autoclaving bag so that the entire unit is autoclaved and ready for use in the operating room.

The initial average gamma activity of each seed varies from 0.3 to 0.7 milligram radium equivalents. This activity depends ultimately upon the length of exposure and the position of the seeds in, and upon the neutron flux of the atomic reactor. By using mgm radium-equivalents the usual Paterson-Parker[4] Radium tables can be used for dosage calculations. The mgm Radium-equivalent values can be converted into mr/hr/m by multiplying by 0.84 or into r/h/cm by multiplying by 8.4 or into mc of Ir^{192} by multiplying by 1.5 (using A.E.C. value of 0.55 mr/h/m per mc Ir^{192}).

At 1 meter from the fully loaded kit the dose rate would be less than 5 mr; or less than 1 mr/hr, 1 meter from the kit in its shipping box. Therefore, accord-

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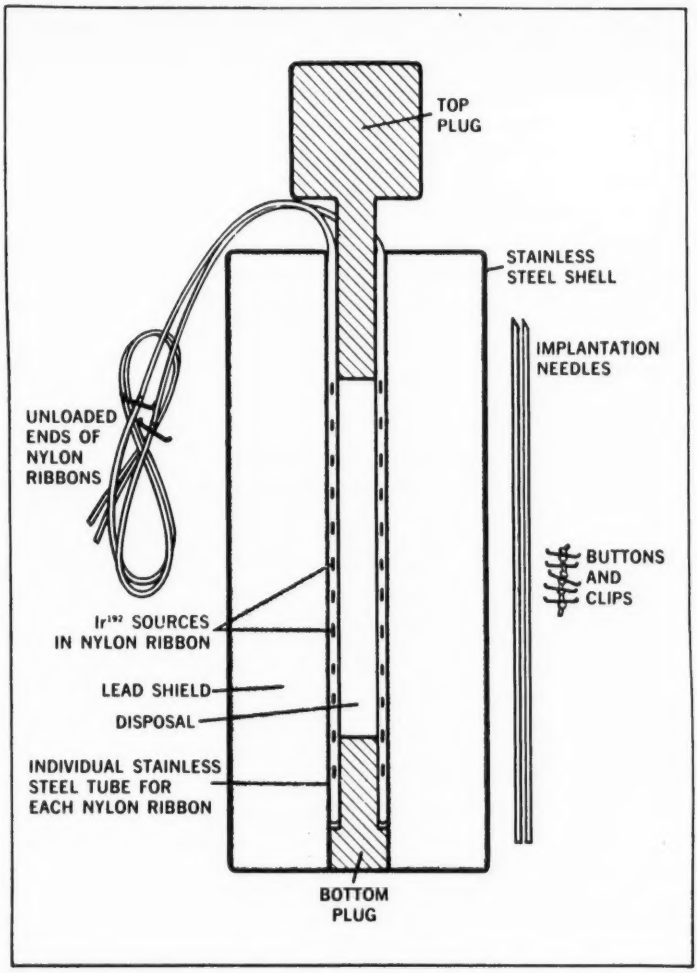
[1]Available from E. R. Squibb and Sons, as "Iriditope Ribbons Therapeutic".



Lead container with Iriditope Ribbons.

Fig. 1. Lead container with nylon ribbon loaded with Iridium^{192} seeds. Container designed by Dr. Ulrich Henschke, Memorial Center, N.Y., as depicted in "Iriditope", Squibb Technical Data Sheet.

ing to A.E.C. regulation the set can be kept on hand without additional shielding provided the box is properly labeled and locked.

2. *Selection of cases for the "Blind End" technique.*

The likelihood of the guide needles perforating bowel precludes the use of this technique except when previous surgery has isolated the viscera above the

peritoneal reflection. Abdominal-perineal resections for carcinoma of rectum especially fulfill this criterion. Therefore, in our initial exploration of the "Blind End" interstitial implantation technique we have limited ourselves to cases of recurrence or persistence following abdominal-perineal resections.

Cases of recurrence following posterior or total pelvic exenteration for gynecological cancers, may also be suitable if isolation of the remaining intestinal contents above the peritoneal reflection has been assured. Bladder penetration by the guide needles presents a special but lesser problem as the description of the technique and case presentation will indicate. However, I do not consider the possibility of bladder penetration as a contraindication to the technique especially if one is cognizent of the possibility and takes appropriate measures when it occurs.

3. *The "Blind End" Technique.*

The patient is anesthetized preferable under general anesthesia and placed in the lithotomy position with the table tilted so that the pelvis lies higher than the abdomen, thereby enabling intestinal viscera if free to do so, to fall away from the implantation field. If the vaginal tract is intact or if a perineal-pelvic cavitation is present an attempt is made to define the extent of the malignant involvement by direct finger palpation of the tumor, even though only a small portion of the recurrence can be delineated in this manner. A truer evaluation of the depth and breadth of the disease becomes more evident upon placement of the implantation needles. The Iriditope kit which had previously been autoclaved is placed as a sterile unit in its autoclaving bag within a sterile draped large stainless steel basin having a wheeled stand. The implantation needles, button-clips are likewise autoclaved and placed upon a simple instrument table along with long thoracic clampas, forceps and scissors. Assistants prepare the kit by rolling down the autoclaving bag in sleeve-like fashion exposing the lead cork which covers the existing inactive nylon ribbon ends. These ends are conveniently coiled and held to the sides of the stainless steel lead container by readily removeable tape. For the "Blind End" technique the meter long inactive nylon ribbon leaders are cut and discarded leaving a sufficient inactive length to facilitate handling and later threading into the guide needles. Then until the active Iridium ribbons are needed the lead cork (Fig. 1,) is kept in place and the entire unit is wheeled off to a safe distance, which is conveniently determined by use of a survey meter. Preceding the implantation a Foley catheter is inserted into the bladder to maintain it in an empty and contracted state. While the kit preparation is being undertaken the therapist is in the process of placing the implant guide needles. Since the guide needle placement does not involve handling radioactive sources the therapist can carefully and accurately introduce or rearrange his guide needle pattern without haste and concern about radiation exposure.

The bony pelvis ultimately controls the depth to which the guide needles are introduced. The first 4 needles introduced are used to outline the circumference of the implant. Each of the four needles are placed at 12, 3, 6 and 9 o'clock. The

peripheral extent of the recurrence can be determined while introducing the guide needles since normal non-cancerous tissue is evident by the ease of introduction and the absence of gritty resistance. When the peripheral extent of the pelvic-perineal recurrence has been so determined (Figure 2,), the needles may be withdrawn and re-introduced more peripherally to ensure inclusion of the tumor and sufficient rim of normal tissue. Thereafter the remaining circumferential guide needles are introduced parallel to the first group of needles and then to one another until their tips strike the hollow of the bony pelvis. (Figure 3,) Having thus identified the deepest depth to which each needle can be inserted, the needles are withdrawn depending upon the estimated depth of tumor involvement. At least slight withdrawal of each needle is necessary to be sure the tips are in soft tissue rather than bone, since fixation of the needle in bone makes

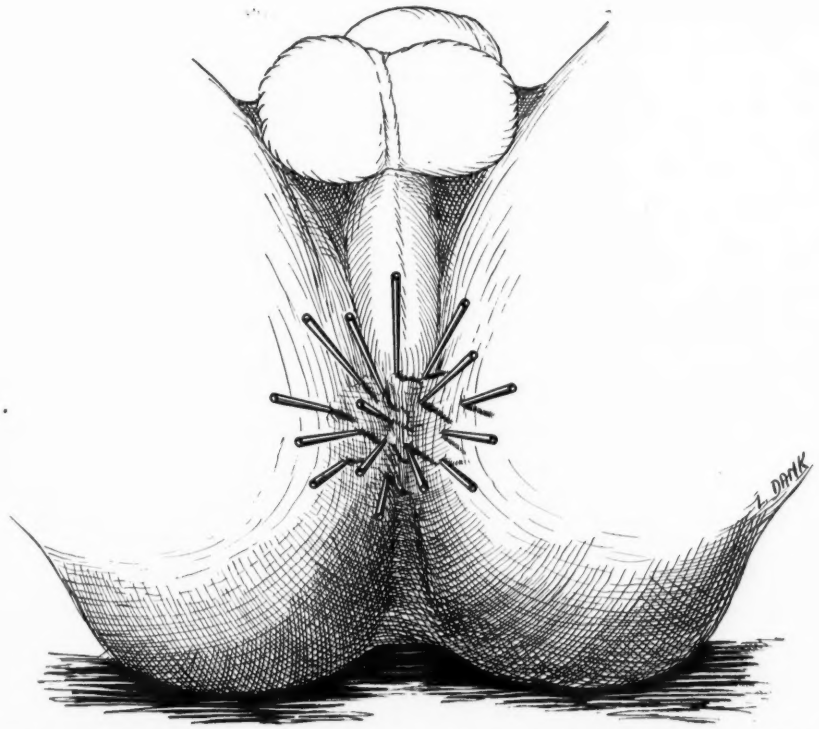


Fig. 2. View of patient in lithotomy position with #17 stainless steel guide needles deeply inserted encompassing the recurrent tumor, located in the perineal-pelvic area. The Iridium seeded nylon ribbons have not yet been threaded.

subsequent withdrawal of the guide needles threaded with nylon ribbon more difficult. Upon the introduction of the various guide needles one may draw blood. Should this occur it indicates entry into a vein or artery. This is a most minor problem and in our experience has never resulted in uncontrolled bleeding

or hemorrhage. Simple slight withdrawal or reintroduction of the needle stops continued bleeding. I have assisted Dr. Ulrich Henschke with permanent Iridium implants and he has shown that entry into vena cava, bronchial vessels and even aorta merely requires withdrawal of the needle tip until bleeding stops or complete reintroduction of the needle. Troublesome bleeding or fatal hemorrhage has never occurred. The introduction of the guide needles is not dissimilar to experience with translumbar aortography. When the circumference of the tumor

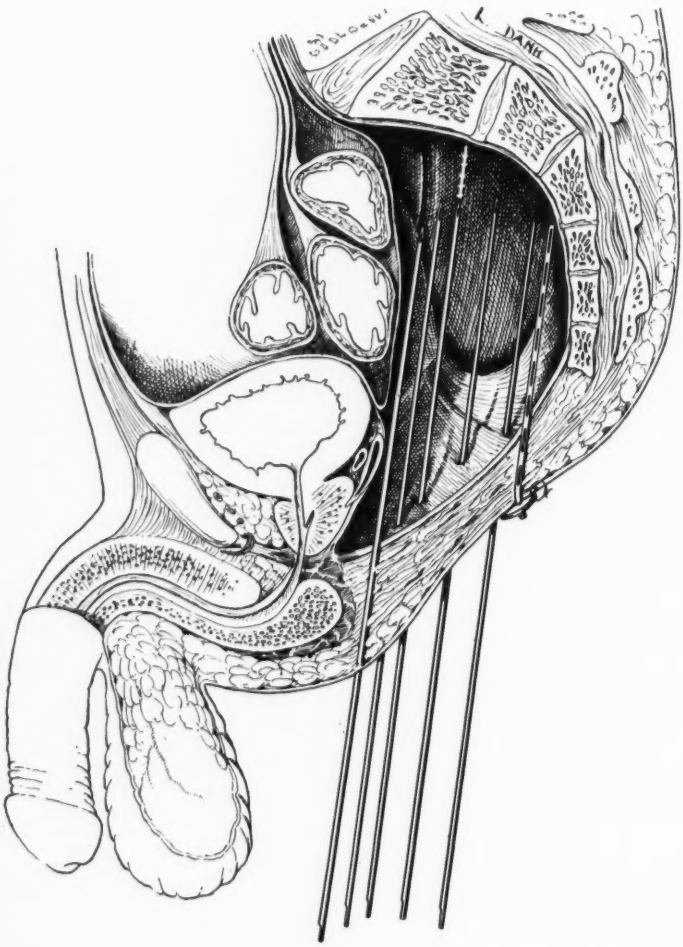


Fig. 3. Sagittal section showing guide needle placement towards hollow of the sacrum. Each needle is introduced to bony pelvis, for orientation, then slightly withdrawn to prevent imbedding in bone. Note the final placement of the Iridium seeded nylon ribbon sutured to the skin through a hole in the button-clip.

has been implanted the therapist procedes with further placement of sufficient needles to fill the core of the volume and by careful placement also aligns these needles to one another, thereby eliminating undesirable crossing or angulation of the radioactive ribbons to be threaded later. The separation between radioactive sources in each ribbon is predetermined in their loading and is 1 cm between their respective centers. The separation between parallel ribbons of radioactive seeds is determined at the time of the implant by the therapist who can vary the distance beween guide needles depending upon the dose desired for an implant time of 7 to 10 days. The choice of needle separation is ultimately dependent upon the individual seed strength and their total number at the time of the implant. A kit loaded with at least 14-12 seeded ribbons and with initial seed activity of 0.3 to 0.5 mgm Ra equivalent will be sufficient for a volume implant of 8 cm diameter allowing for 1.0 cm guide needle separations. As Shalek[5] has demonstrated, for larger volumes, uniform distribution of radioactive source of uniform activity suits the criteria of the Paterson-Parker distribution rules in sofar as the number of mgm hours needed to deliver each 1,000r for a given volume. Furthermore, the Iridium seed ribbon technique reasonably satisfies the Paterson-Parker distribution rules as regards the proportion of the total activity in the "rind" and "core" respectively as well as its recommendations as to numerical number of line sources in the "rind" or circumference of the volume implant.

As the implant is being completed accuracy and spacing of placement is checked and needles withdrawn and reinserted as deemed necessary. When the pattern of needles is completed minimal oozing of blood may be noted in some needles but if not brisk further manipulation of the needles is unnecessary.

After the placement of the guide needles has been completed, an assistant uses a long Kelly or Kocher clamp to grasp each guide needle at its protruding end in order to steady them thereby facilitating threading them with radioactive ribbons. The Iridotope kit is now rolled to the side of the therapist and the lead cork carefully removed. The therapist determines the active length of the Iriditope ribbon that will be required by using sterile centimeter ruler. The overall length of the needle is known so that by subtracting from the overall length of guide needle the length protruding beyond the skin the actual depth of the needle in the patient is determined. This length is the active length of the Iriditope ribbon to be inserted. Most needles placed in the perineal-pelvic tissue will accept the full active length of the ribbon, with an overall active length of 13 cm. To ensure that sufficient inactive ribbon protrudes from the skin after the ribbon has been threaded and its styleted needle withdrawn, the inactive nylon ribbon end is cut three to four centimeters longer than the active length. The Iridium loaded nylon ribbons used for threading are grasped by the therapist with a long thoracic clamp and pulled from their respective channels in the lead container. After the ribbons are withdrawn from the lead container they are cut to length, dependent upon the depth of the imbedded guide needles. Should fewer than the 12 Iridium seeds be needed for threading a guide needle, the active end of the ribbon containing the excess seeds is cut off and stored in the lead container's central storage space.

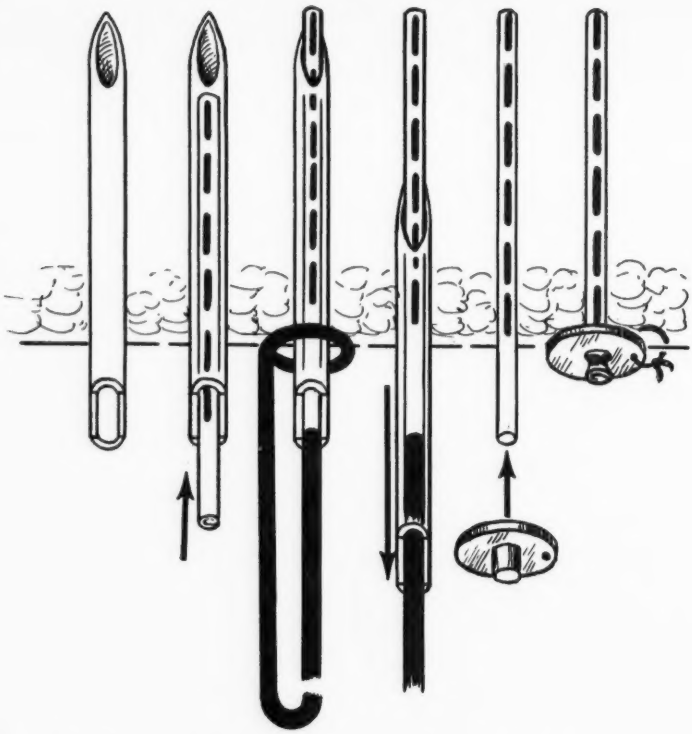


Fig. 4. Steps to be followed in the threading of guide needles with Iridium^{192} seeded nylon ribbons.

Figure 4, shows the detail steps to be followed in the threading of the guide needles with the Iridium seeded nylon ribbons. The 0.5 cm hemi-cylinder machined grooved head of the guide needle facilitates the initial threading of the nylon ribbon. Without this groove, threading time and hence personnel exposure is considerably greater. The ribbon is then threaded down the guide needle until its inactive end lies just within the hemi-cylinder grooved guided needle head. Each ribbon whose length is predetermined by each needle depth, is slowly further advanced along the 30 cm guide needle by the after following stylet. If a simple straight stylet is used care must be taken not to advance it into the guide needle more than the depth of the implanted part of the needle, making sure there is three to four centimeters of inactive end in the guide needle so as not to completely imbed the nylon ribbon. This is a crucial point in the technique when using a straight stylet since it is necessary to prevent 1) the inadvertent withdrawal of the ribbon or 2) the complete loss of the nylon ribbon deep into the tissues. As illustrated in Figure 4, (exit arrow), Dr. Ulrich Henschke's newly designed double-limbed loop stylet will prevent either of these two eventualities from occurring. The outer limb of the looped stylet is the length of the guide

needle, whereas the limb acting as the stylet within the needle bore is 2 cm shorter than the overall guide needle length. The double limbed stylet is immobilized against the skin surface by its loop and can neither be advanced nor withdrawn; contrariwise the guide needle itself is completely withdrawn from the tissues over the exposed stabilized stylet in a sheath-like action. The final extraction of the guide needle tip from the skin results in a sufficient length of inactive nylon ribbon existing from the skin. The nylon ribbon is now secured to the skin in the fashion shown in Figures 3, 4. The button-clip whose cylindrical projection is crimped fixes the nylon ribbon. The button contains a hole at its periphery to facilitate suturing it to the skin. When all guide needles have been withdrawn and each nylon ribbon has been secured to the skin, a simple perineal dressing is applied. A Foley catheter is always placed in the bladder.

Fig. 5. Patient W.S., male, age 37. Recurrent rectal Adenocarcinoma following abdominal-perineal resection. X-ray shows implanted perineal-pelvic recurrence. Two Iridium[192] seeded nylon ribbons seen high in the pelvis were inadvertently inserted into the abdominal cavity. Note the button-clips fixing the ribbons to the perineal skin.

4. *Special problems related to the technique.*

Patients tolerate the procedure well. No local infection at the skin implantation site or deep pelvic cellulitis arising along the ribbon tracks has been met

with. Neither has uncontrolled hemorrhage or late hematoma occurred. In one patient (W.S.) the inactive ends of two Iridium seeded ribbons were inadvertently completely imbedded in the perineal tissue as the guide needles were being withdrawn. This occurred before appropriate stylets were designed. Even with local incision at the needle site it was impossible to isolate the ends. Localization films (Fig. 5,) revealed that two laterally placed ribbons were deeply imbedded and lying superior and anterior to the main implant. It was suspected that they had entered the general abdominal cavity. This fact was confirmed at autopsy 4 months later when the two seeded nylon ribbons were recovered from the peritoneal cavity.

No local bowel reaction or perforation was noted at autopsy, nor was there any evidence of local inflammatory reaction of the omentum about the nylon ribbons, which were freely lying amidst small bowel. This vividly attests to the inertness of the nylon tubing. The patient had succumbed to his disease unrelated to the procedure. Patient (W.S.) also had transient mild hematuria the first day post-implantation. We surmised that an implantation guide needle may have penetrated the bladder and wished to make sure that it did not contain a seeded

Fig. 6. Patient J.C., female, age 46. Recurrent rectal Adenocarcinoma following abdominal-perineal resection. Vaginal canal present. X-ray shows combined Radium Tube-Iridium^{192} nylon ribbon implant of vaginal-pelvic recurrence. Note the collection of Iridium^{192} seeds at left sacral area, predetermined at the time of implantation.

ribbon. Cystoscopy revealed a linear superficial needle tract in the bladder base to the right of the mid-line. No nylon ribbon was present. The remainder of the bladder was normal. This tract in the bladder was caused by one of the most anteriorly placed guide needles. The tract subsequently healed completely. A Foley catheter was kept in place for the next week without further complications. The presence of the two Iridium^{192} seeded nylon ribbons in the abdominal cavity

Fig. 7a. X-ray of same patient (J.C.) demonstrating how implant can be adjusted from the previous pattern in Figure 6, to that shown here.

required that instruction be given to the patient (W.S.) as to the allowable exposure to others near him. A printed form giving permissible exposure times to others was given to him. Fortunately he was unmarried and lived alone. The initial activity was .294 mgm-Radium equivalence per seed for a total of approximately 7.1 mgm-Radium equivalence for the two ribbons (12 seeds in each). Two weeks following the Iridium^{192} implant removal, the permanently imbedded seeds gave a dose rate of 1.5 mr/hr at 1 meter, and 3 mr/hr, at contact in the lower abdomen. No subsequent radiation syndrome or hematological depression was noted.

Figure 6, shows a combined Iridium[192] seed nylon ribbon pelvic implant and radium tube insertion in another patient (J.C.) who had massive vaginal tract and left hollow of the sacrum recurrence following abdominal-perineal resection for rectal cancer. It should be noted in Fig. 6, that ribbons on the left side of the implant had sufficiently long inactive ends so that the seeded portion could be advanced deeply to form a desired implant at the deep hollow of the sacrum region. The calculation of dosage necessitated a construction of two volumes, the vaginal portion and deep pelvic portion. By the earlier differential extraction of the radium, the vaginal area received 5,000r from the radium-iridium combination; the deep pelvic area received 6,500r from the Iridium implant itself. Patient J.C. survived 15 months from the time of the implantation procedure.

Fig. 7b. Lateral view of adjusted implant. Note the depth of Iridium[192] seeded nylon ribbons in relation to the sacral hollow.

5. *Ease of adjusting the implant.*

Figures 7a and 7b, show in anterior-posterior and lateral views the position of the Iridium seeds in the same patient (J.C.) prior to the final removal of the ribbons. I include these x-rays to demonstrate the ease with which the depth of the seeded ribbons can be adjusted to assure a better implant distribution, should a localization film indicate the need for such a modification. This is accomplished

in the examining room without anesthesia, by simply shortening the ribbons which have been too deeply placed.

Conclusion.

Inaccessible deep pelvic tumor recurrences following abdominal-perineal resections for cancer of the rectum can be readily implanted with the "Blind End" technique, using commercially available removable nylon ribbons, loaded with radioactive Iridium^{192} sources. Refinements in the technique are presented which if followed should result in optimal volume implantation with minimal complications.

ACKNOWLEDGEMENT

I wish to thank our physicist, Normand J. Michaud, B.S., for his assistance during the operative procedures and for his suggestion for machining of the hemi-cylinder grooved guide needle heads.

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JOURNAL OF NUCLEAR MEDICINE 3:268, 1962

Stability Studies on I^{131}-labeled Albumin[1]

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Radioactive iodinated human serum albumin has been known for some time to be a clinically useful tracer. It is widely accepted in the estimation of blood and plasma volumes and has been employed in localization studies. It is commercially available in sterile, pyrogen-free isotonic solution.

Wasserman et al (1) (2) (3) demonstrated in animals that the rate of disappearance of the radioactive iodinated serum albumin (RISA) from blood can be characterized as a two-part exponential curve. The first portion of the curve represents the dilution phase in which tagged albumin diffuses out of the vascular bed into the extravascular spaces and the second phase represents metabolic breakdown of the tracer. Their work suggested that the method might be applied to the study of the rate of protein turnover in humans (4) (5) (6).

Radioactive iodinated human serum albumin was administered intravenously to 12 subjects in single doses of 10 to 20 microcuries. Blood samples were obtained on the first day at 30 min., 1 hr., 6 hrs., and 12 hrs. after injection and once daily for the following five to eight days. Total protein estimations and separation of albumin fraction were done in routine fashion. The data is plotted as the logarithm of the specific activity of the plasma albumin against time as shown in Figure 1. This represents a typical two-phase exponential curve which is the composite curve on the observed 12 patients. In this study the metabolic half time (T ½) of iodinated albumin is about 9.8 days which is shorter than the results reported for normal adults (4) (5) (6). Reported values for T ½ vary from 10 to 27 days.

If one assumes accuracy in technique and instrumentation, it is apparent that the validity of the measurements depends on the stability of the tagged tracer material. Not only is the rate of protein degradation important but loss of radioactive iodine from the intact albumin moiety could invalidate measurements of metabolic turnover. If separation of the iodine tag occurs, then the value for

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[2]Aided by a grant from the John A. Hartford Foundation.

specific activity would be altered in a manner unrelated to metabolic turnover rate of protein. It is possible for I^{131} ion to attach to albumin in solution. When I^{131} ions (1.0 mc/cc) were added to a solution of albumin (10 mg/cc) and incubated for 12 hrs., followed by 48 hour dialysis against saline about 5 per cent of the I^{131} remained bound to albumin. It is unknown whether such "tagging" can occur in vivo but such rejoining of protein and I^{131} could give false high values for specific activity. Similar evidence has been cited by Berson (4). In all freshly tagged albumin preparations about 3 per cent of the tag was dissociated or "free" from the accompanying protein.

Two procedures, dialysis and protein precipitation were set up to estimate the rate of radioiodine separation and the rate of protein degradation with time. In the dialysis procedure, a uniform lot of commercially available I^{131} labeled albumin was placed in stationary dialysis against saline solution. Asepsis was maintained throughout. Evaporation was prevented by parafilm covers. The concentration of I^{131} ion was corrected for diffusion into the total volume inside and outside the bag. Protein concentration was corrected for dilution by dialysis fluid. Ten to twelve mg of albumin per cc containing one mc radioactivity per cc were diluted to 5 cc with saline and dialysed against 10 cc of saline. Dialysis

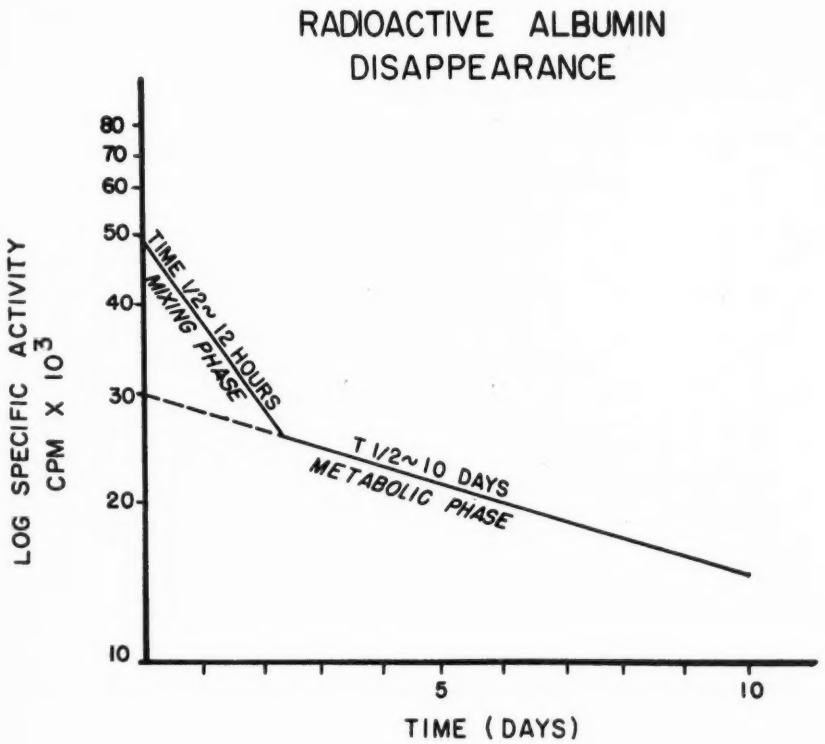

Fig. 1

was carried out at 37° C. for 15 days. Aliquots for the bag content and dialysate were assayed for protein content by the biuret method and for radioactivity in a well scintillation counter. The composite curve of seven runs is charted in Figure 2. At the end of 15 days, 33 per cent of the iodine tag was "free" and some 10 per cent of the protein had disappeared. These data indicate that marked radioiodine tag loss occurs during the time that moderate protein change is occuring and support the observations of Margen and Tarver (7) who demonstrated that the assumption that loss of iodine tag is a measure of protein degradation is erroneous.

In the protein precipitation experiments, sets of test-tubes containing equal amounts of I^{131} labeled albumin were allowed to stand under aseptic conditions at 37° C. At intervals of three days and then at weekly intervals, the protein in duplicate tubes was precipitated by one volume of 10 per cent trichloracetic acid. The supernatant liquid was found free of protein. Control experiments with the sodium salt of trichloracetic acid in equal concentration failed to show interference with the biuret reaction. The radioactivity of the supernatant liquid is thus a measure of separation of iodine label. Figure 3 illustrates typical data obtained at 37° C. The original tagged albumin solution showed 766,000 counts per ml per minute. At the end of 40 days 230,000 counts per ml per min. were present in the supernatant liquid when corrected for dilution by added trichloracetic acid. Thus approximately 30 per cent of the radioactivity was no longer associated with protein.

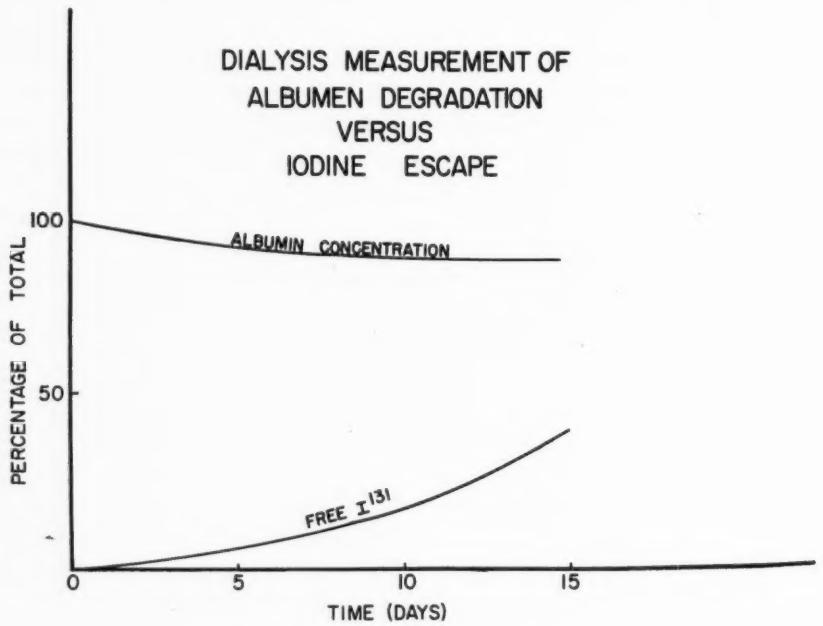

Fig. 2

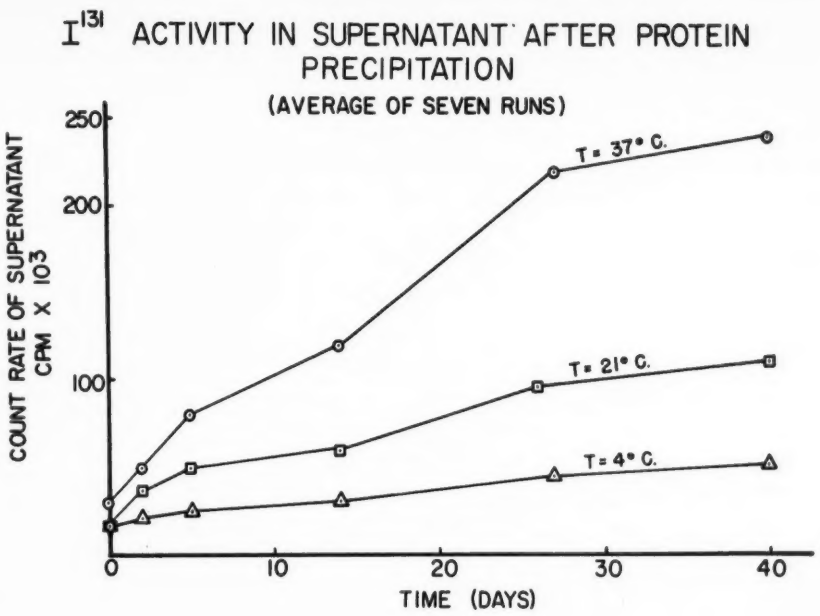
I131 ACTIVITY IN SUPERNATANT AFTER PROTEIN PRECIPITATION
(AVERAGE OF SEVEN RUNS)
COUNT RATE OF SUPERNATANT CPM X 103
250
200
100
T = 37° C.
T = 21° C.
T = 4° C.
0
10
20
30
40
TIME (DAYS)

Fig. 3

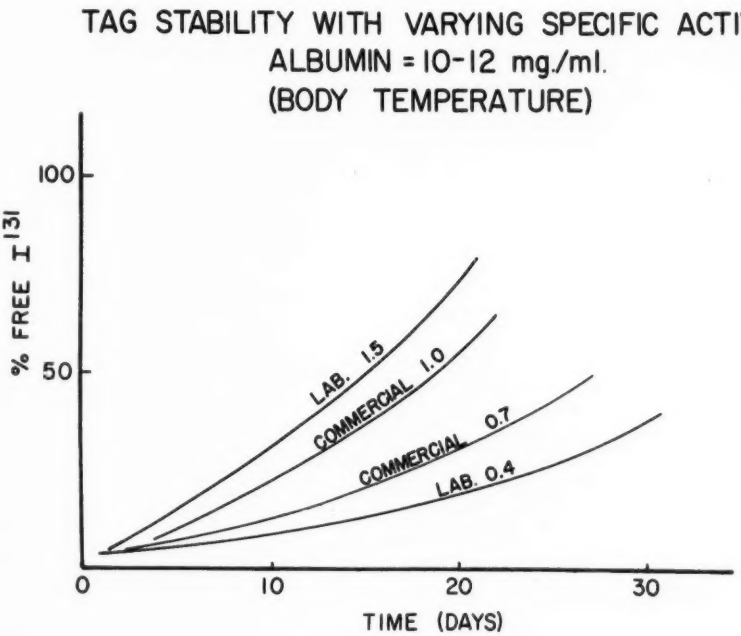
TAG STABILITY WITH VARYING SPECIFIC ACTIVITY
ALBUMIN = 10-12 mg./ml.
(BODY TEMPERATURE)
% FREE I131
100
50
LAB. 1.5
COMMERCIAL 1.0
COMMERCIAL 0.7
LAB. 0.4
0
10
20
30
TIME (DAYS)

Fig. 4

The effect of temperature on iodine tag separation was studied, using the protein precipitation technique at 4° C., 21° C. and 37° C. (Figure 3). The data indicate that the rate of separation of I^{131} from albumin is a function of temperature and time. At 37° C. for 40 days the separation of I^{131} tag (30 per cent) is six times greater than it is at 4° c. (5 per cent).

To determine the effect of specific activity of radioalbumin on loss of iodine tag, iodinated albumin of various specific activities (0.4 and 1.5 mc/ml) was prepared in our laboratory.[1] Commercial preparations of specific activities 0.7 and 1.0 mc/ml were tested. The experiments were carried out at 37° C. and the separation of I^{131} from albumin was measured in the supernatant liquid of a trichloracetic acid precipitation of protein as indicated above. In all cases, the protein concentration was the same but the specific activity varied. The separation of iodine tag appears to be a function of specific activity and time (Fig. 4). This finding has been reported by others (8) and it has been asserted that the integrity of the protein molecule is altered by radiation.

SUMMARY

It has been shown that "low specific activity" albumin is more stable than high specific activity albumin at any temperature from 4° C. to 37° C. Even low specific activity albumin loses significant amounts of iodine tag after 8 to 10 days at 37° C. The results of these studies would seem to question the value of this tracer in long term albumin turnover studies.

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[1]We wish to thank the American Red Cross for their generous donation of human albumin.

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Three New Test Agents for the Radioisotope Renogram: DISA-I^{131}; EDTA-Cr^{51}; and Hippuran-I^{125}

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Several test agents are available presently with which satisfactory radioisotope renograms may be obtained, e.g., Hippuran-I^{131} and Hypaque-I^{131} (1, 2). The property of excretion exclusively by the kidneys is common to most of these agents but they vary in the rates of clearance from the blood. One of them has an undesirable quality for the test due to excretion by the biliary system also, i.e., Diodrast-I^{131} (3). In keeping with progress in this field, results of studies with three new test agents are herewith reported. Table 1 lists some of the properties of all renogram test agents known to date in regard to desirability and disadvantages. In addition, the tenth labeled substance, now undergoing evaluation in this laboratory, is postulated to be the agent of choice at the present time.

2, 6-Diiodosulfanilate Labeled with Radioiodine-131; DISA-I^{131}. This compound was found by Myers (4, 5) to have low toxicity in mice and to be cleared rapidly in the urine after intravenous injection. The clearance halftime in man was found to be about an hour.

Since the compound can be labeled readily with radioiodine isotopes by simple chemical synthesis (6), in good yield, and with high specific activities, it was prepared here and studied clinically as a potential renogram test agent. Twenty-one DISA-I^{131} renograms were performed among 17 patients who also had Hippuran-I^{131} renograms, urinalyses, intravenous urography, blood urea nitrogen, serum creatinine, and phenolsulfonphthalein (PSP) determinations. In addition, some of these individuals had aortography, 30 minute urine clearance for the renogram agent, blood clearance tracing for the renogram agent and individual renal clearance tests.

The labeled DISA was found to be cleared from the blood more slowly by the kidneys of patients than in the case of mice. Also, the function and the ex-

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[1]Assisted technically by Eleanor Poehlmann, M. A. and Nancy Steinecker, R. N.

Departments of Surgery (Urology), Medicine and Radiology, Ohio State University Health Center, Columbus, Ohio. Presented before the Society of Nuclear Medicine, Pittsburgh, Pa., June 17, 1961.

TABLE 1

AGENTS	ADVANTAGES	DISADVANTAGES
Urokin-I^{131} Sodium-I^{131} DISA-I^{131}		Slow renal clearance.
Diodrast-I^{131}	Rapid renal clearance.	Also hepatic excretion.
Miokon-I^{131} Renografin-I^{131}	Moderately rapid renal clearance.	
EDTA-Cr^{51}	More economical. High "Photon Merit Ratio".	Slow renal clearance.
Hypaque-I^{131} Hippuran-I^{131}	Rapid renal clearance.	
Hippuran-I^{125}	Most rapid renal clearance. Most economical. Highest "Photon Merit Ratio".	

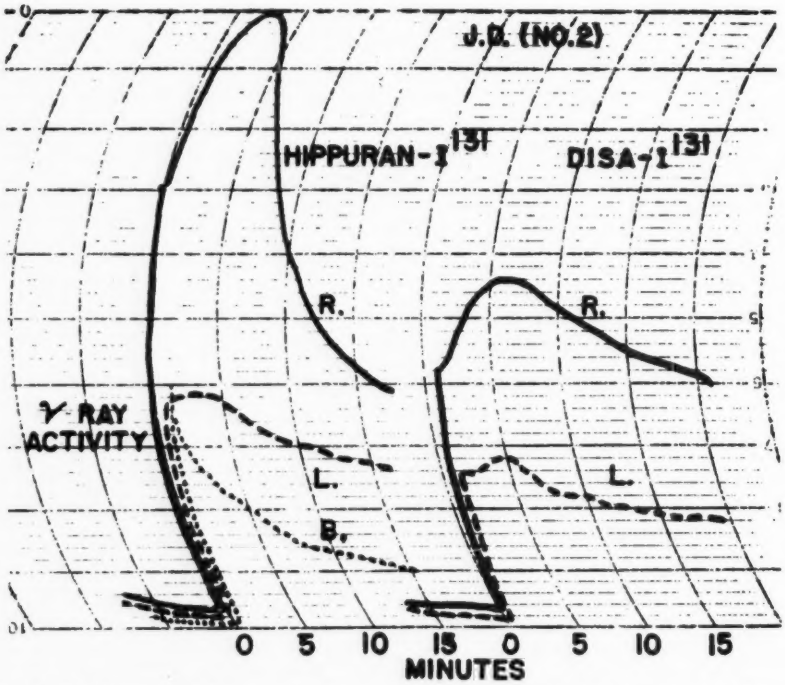

Fig. 1. The Hippuran-I^{131} renogram shows a classically normal right tracing and decreased vascularity and function on the left side. The blood clearance[B] is normal, indicative of normal *total* renal function. The DISA-I^{131} renogram of the same patient shows less amplitude of all segments with a slower rise and fall of the functional and excretory segments respectively.

TABLE 2

Patients	*Total Renal Function*	*15 Minute Blood Clearance (%)*			*30 Minute Urine Assay (% Recovery)*		
		Hippuran-I^{131}	DISA-I^{131}	EDTA-Cr^{51}	Hippuran-I^{131}	DISA-I^{131}	EDTA-Cr^{51}
		Normal over 45%			Normal over 65%		
1. K. S.	Normal	63				35	
2. J. D.	Normal	53				32	
3. W. M.	Normal					26	23
4. S. W.	Normal	47–52				16	
5. L. D.	Normal	47	33			16	
6. W. G.	Normal	48					
7. R. H.	Normal	59					
8. P. N.	Normal	47–52					
9. C. C.	Normal	47					5.5
10. F. S.	Normal						
11. H. K.	Slight Azotemia	41–42				12	
12. A. R.	Slight Azotemia		23			8	
13. T. S.	Moderate Azotemia	26–33		15	40		2
14. R. S.	Moderate Azotemia		13			3.5 –4	

cretory segments of the DISA-I^{131} renogram changed more slowly and with less amplitude than with Hippuran. No accumulation of radioactivity in the liver or thyroid gland was observed. Values for blood and urine clearances are shown in Table 2. Typical normal renograms with DISA-I^{131} and Hippuran-I^{131} are shown in Figure 1 (patient # 2, Table 1). Comparable renograms in a moderately azotemic patient are illustrated in Figure 2.

Radiochromium-51 Chelated with Ethylenediamine Tetraacetate: EDTA-Cr^{51}. This "photon carrier" compound was found by Myers and Diener (7) to be excreted in the urine of rats after injection intravenously, with a biological half-time of about 15 to 20 minutes. This was thought to be the first time a radioisotope other than I^{131} had been utilized for renography. The long "shelf-time" of Chromium-51 due to the physical half-life of 28 days makes for convenience and economy in comparison with I^{131} with a physical half-life of only eight days. Furthermore, Cr^{51} emits a single 323-kev γ-ray and no undesirable β-particles. Consequently it has a high "photon merit ratio" (= "usable" signals/absorbed energy).

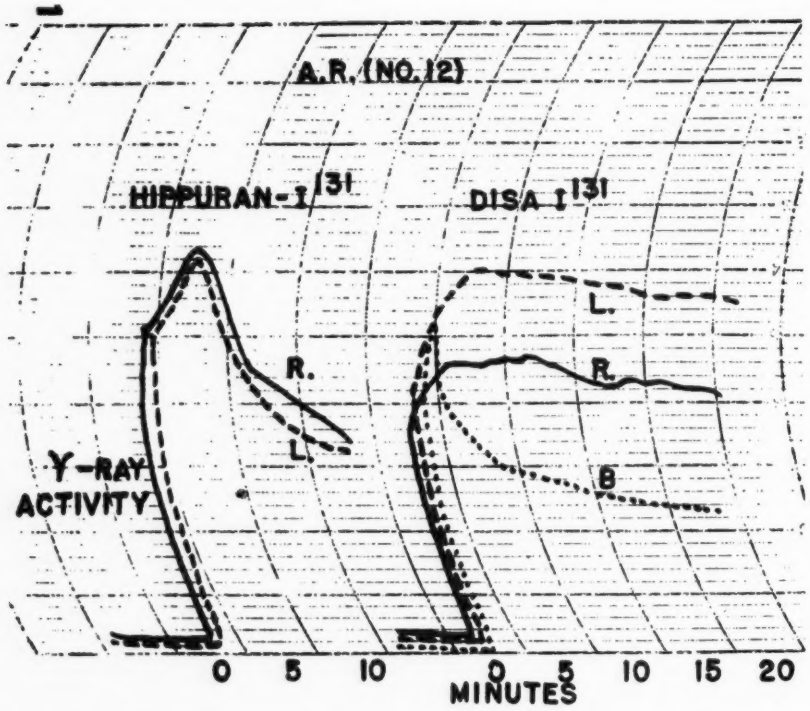

Fig. 2. The Hippuran-I^{131} renogram of the moderately azotemic patient shows slower, shorter functional segments. The DISA-I^{131} renograms in the same patient show prolonged functional segments that descend only slightly. The blood clearance tracing shows a slow rate of fall.

Clinically, it became apparent at once that EDTA-Cr^{51} was cleared from the blood relatively slowly by human kidneys. Although there was no evidence of accumulation by other organs, the 30-minute urine assay in two normal patients averaged 14 per cent and was 2 per cent in a moderately azotemic patient. The latter compared unfavorably with 40 per cent recovery of Hippuran-I^{131} in the 30-minute urine of the same patient. Figure 3 shows that the functional and excretory segments of the EDTA-Cr^{51} renogram changed slowly and with low amplitude. These clinical findings may indicate a labile attachment of EDTA-Cr^{51} to plasma proteins that then becomes detached and cleared by the kidney with a half-time of 2-3 hours (8).

In a previous communication (1) it was postulated that the ideal renogram test agent should be: "1) stable chemically; 2) resistant to heat; 3) easily prepared; 4) inexpensive; 5) non-toxic; 6) cleared rapidly from the blood solely by the kidneys; and 7) not accumulate or become localized in any other organ".

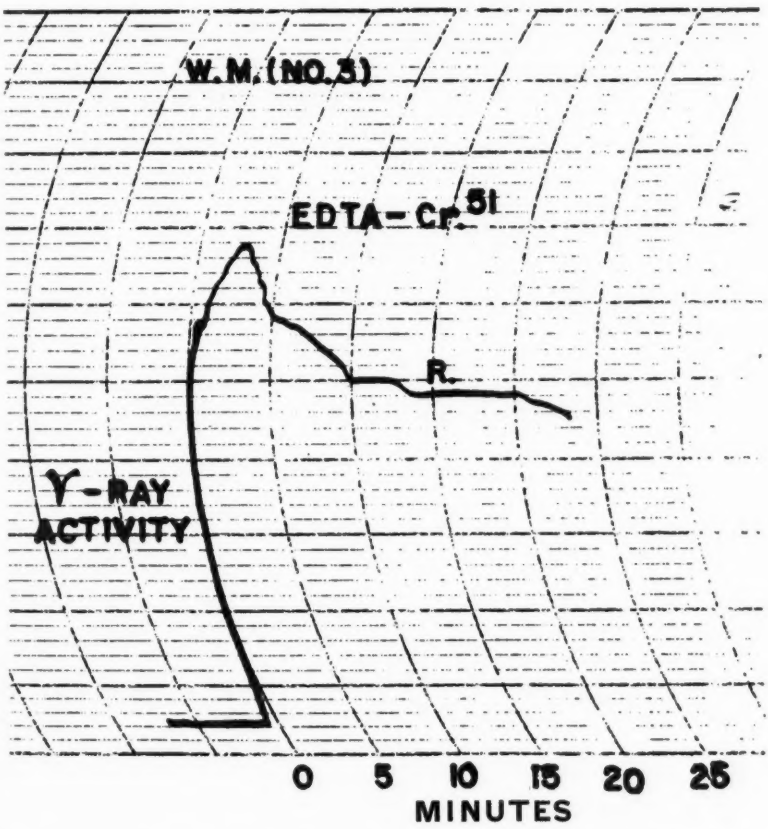

Fig. 3. The normal EDTA-Cr^{51} renogram shows a short functional segment with a slow excretory phase indicating slow renal clearance of this test agent.

Despite this array of desirable qualities, inadequate attention was focused on the physical properties of the radioisotope used to label the test compound. It is now apparent that radioactive isotopes other than I-131 probably may be utilized advantageously (9). Radiochromium-51 has a more favorable half-life of 28 days from the standpoint of convenience, but it cannot be attached chemically to the contrast media that are currently the test agents of choice. The single 323-kev γ-ray lends itself to external counting with detectors and lead collimators now in common use for "photon projection analysis" by means of I^{131}. The absence of useless and undesirable β-particles greatly reduces the radiation exposure per disintegration.

Chelated complexes of Cr^{51} other than with ethylenediamine tetraacetate are currently under study in this laboratory that may prove to be more suitable for making renograms (10).

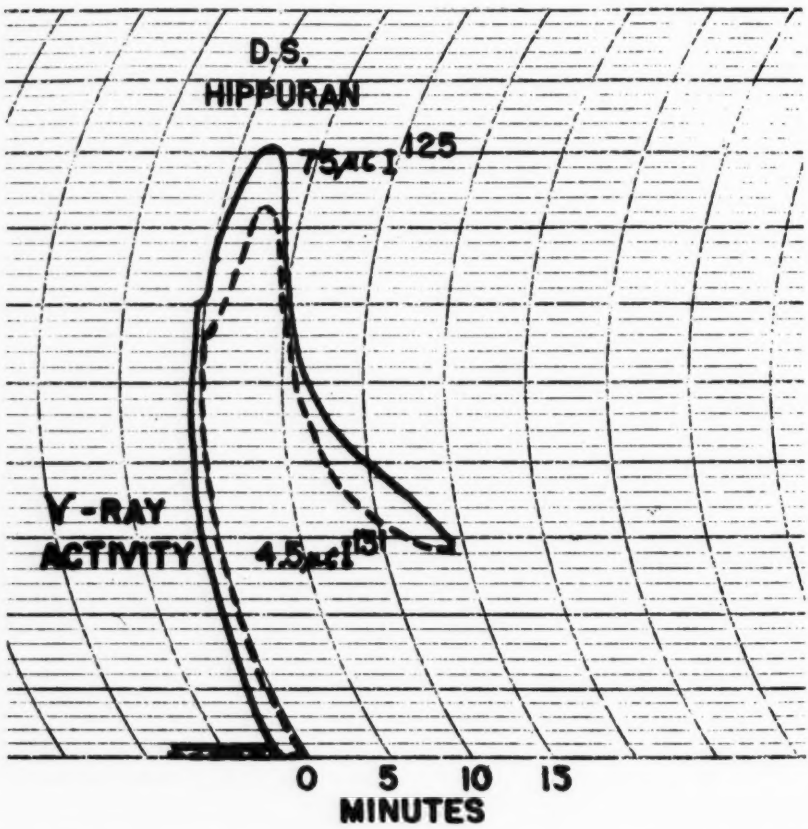

Fig. 4. The Hippuran-I^{125} renogram with standard equipment (one inch crystal and thick lead collimation) appears similar to the I^{131} Hippuran tracing in this normal patient. However, a 16 fold increase in dosage was necessary.

Hippuran-I^{125}. This is the third new test agent now undergoing clinical trials for use in renography in this laboratory. Labeled Hippuran is presently considered to be the "photon carrier" compound that is cleared most rapidly from the blood by the kidney. Radioiodine-125 was discovered in 1946 by Reid and Keston (11) at the College of Medicine of New York University. A study of its advantageous physical properties for clinical applications was reported in 1960 by Myers and Vanderleeden (12, 13). It emits X-rays and γ-rays with usable energies of 27.2-35.4 kev that have a "broad beam" half attentuation in water and soft tissues of the order of almost 1 inch. The low energies of the I^{125} photons permit thin detector crystals to be used so that backgrounds are low and consequently dosages can be smaller. Also, the detectors can be much lighter and collimators less bulky than when a "photon carrier" compound is used that is labeled with an emitter of hard γ-rays, e.g., Hippuran-I^{131}.

A second renogram may be obtained immediately after use of a compound labeled with I^{125} by covering the crystal with a 0.01 inch lead foil to absorb the soft I^{125} photons before using the same or another compound that is labeled

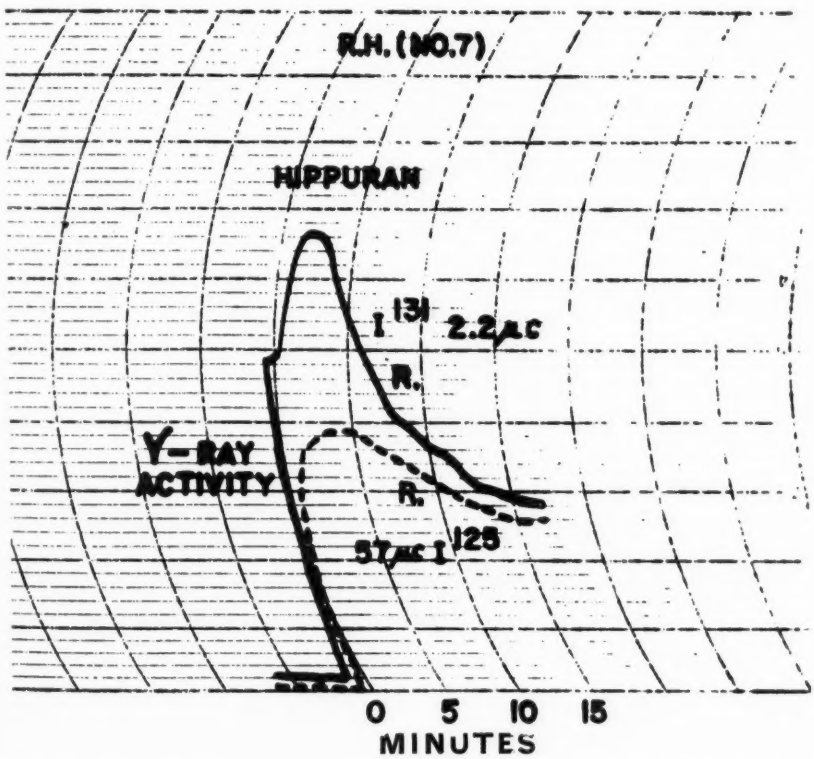

Fig. 5. The Hippuran-I^{125} renograms with a 3/4 inch crystal and 1/100 inch lead foil collimation appears less favorable compared with the standard I^{131} Hippuran record. Again a 25 fold increase in dosage was necessary.

with I^{131}. Alternatively, a spectrometer may be used easily to "tune out" the I^{125} photons in the presence of an emitter of photons of higher energy. A Hippuran-I^{125} renogram obtained with a 1 X 1 inch crystal and lead collimator but without a radiation analyzer is shown in Figure 4. The Hippuran-I^{125} renogram obtained with the 0.5 cm crystal and spectrometer described previously (13) is shown in Figure 5. Finally, a Hippuran-I^{125} renogram is shown in Figure 6, utilizing a 2 X 50 mm crystal and a 0.05 inch lead-foil collimator without a spectrometer.

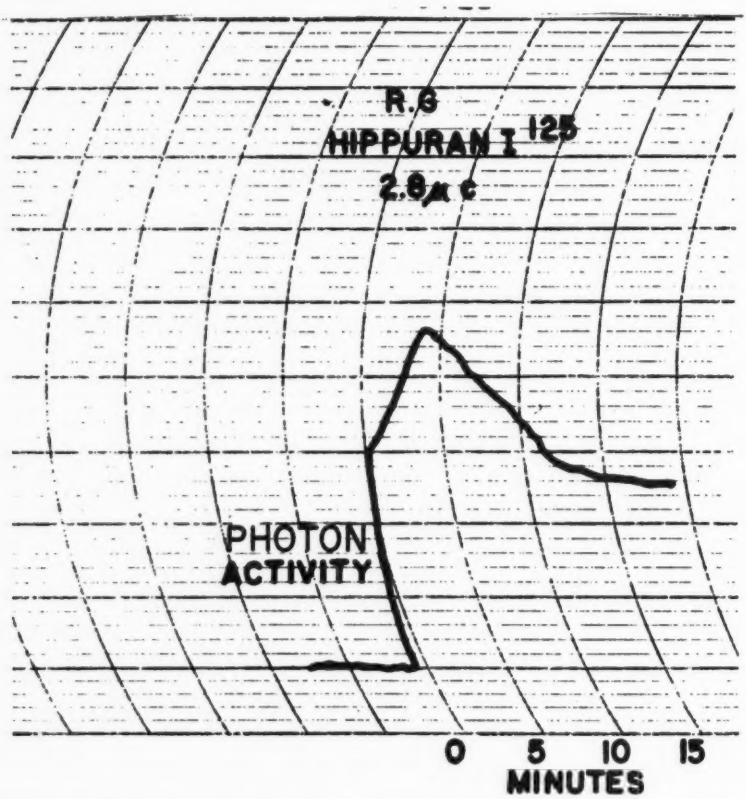

Fig. 6. The Hippuran-I^{125} renogram was made with a 50 x 2 mm crystal and a 0.05 inch lead foil collimator having 1½ inch retraction and an oval window 2 x 1½ inches in diameter.

SUMMARY

Studies on three new radioisotope renogram test agents are reported. DISA-I^{131} and EDTA-Cr^{51} are excreted too slowly by the kidneys to be useful clinically for making standard renograms. Although the ethylenediamine tetraacetate complex labeled with radiochromium is not a suitable "photon carrier" compound for the purpose, Cr^{51} has desirable physical properties for the test

from the standpoint of reducing radiation exposures, convenience and economy. It is the first radioisotope other than I^{131} to be tried in renography.

Hippuran-I^{125} is found to be the test agent of choice at the present time, when used in conjunction with detectors and circuitry that are optimally matched to exploit fully the superior physical properties of radioiodine-125. As the third radioisotope to be used clinically in renography, it will make desirable the first major simplification of the equipment. Light detectors incorporating thin crystals that have low backgrounds, light metal collimators having little bulk, and simple spectrometry are important advantageous features for use of the 27.2-35.4 kev photons emitted by I^{125}.

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Quantitation of Menstrual Blood Loss: A Radioactive Method Utilizing a Counting Dome[1]

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Exact quantitation of menstrual loss of blood is desired frequently by gynecologists, but more frequently by the hematologist. Sometimes a woman presents hypochromic iron-deficient anemia typical of the anemia of chronic blood loss but without detectable abnormal loss. Through exclusion, the physician concludes that the blood loss is menstrual, only to be assured by the patient that her menses are "quite normal."

Since the perineal pads used by most women in this country are capable of retaining surprisingly large quantities of blood, and since women, in general, do not compare their pads, such a declaration of normalcy by the patient should be disregarded by the physician. Nevertheless, the burden of proof rests with him: there are situations wherein he must demonstrate menorrhagia.

TECHNICAL DIFFICULTIES

To do so has always presented some problems of offense to esthetic feelings; but beyond that, the inaccuracy of simple procedures has rendered routine quantitation infeasible.

The reason most procedures are inaccurate is that menstrual blood is spread irregularly through the menstrual pad and that such geometric unevenness, matching poorly with the spatial pattern of equal receptivity (isosensitivity curves) of the usual diagnostic counting equipment of radioisotope laboratories, makes for wide variation in the counting rate.

The reasons for this variation in counting rate are shown in Figure 1. A point source of radioactivity, placed alternately at A and B, will yield net counting rates which differ as much as 100 per cent over some crystals (67 per cent with equipment in the laboratory here)—errors which are, of course, intolerable. The-

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[1]Read at the meeting of the Society of Nuclear Medicine, Pittsburgh, Pennsylvania, June 14 to 17, 1961.

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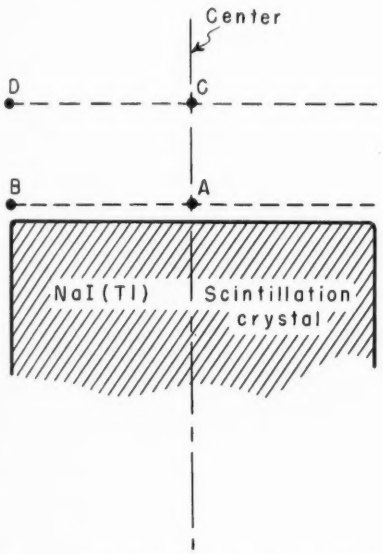
oretically this might be avoided if one could count a comparative standard having the same distribution, but the deposition of blood on the pad is far too irregular for that.

The percentage difference in count rate can be reduced to about 10 per cent by elevating the sample to C and D, 6 or 8 cm above A and B, yielding a maximal error which conceivably approaches acceptability. Unfortunately, the increase in distance between source and crystal so decreases ratio of counting rate to background that one must give far higher radioactivity doses to patients or count for periods so long as to render the whole procedure exorbitantly time consuming—and still without hope of decreasing the error between the C and D locations. This is a discrepancy one would wish to eliminate if possible, especially if a long period has been devoted to the count.

DESIGN OF NEW EQUIPMENT

To minimize the error described, we have developed a counting dome that exactly duplicates the isosensitivity curves of the crystal and eliminates count-rate errors due to geometric irregularity of the sample.

It was designed in the following way. First an accurate isosensitivity curve was obtained over the counting crystal. To facilitate this, a lucite disk was made and etched with concentric circles 1 cm apart and crisscrossed with four diameters (eight radii) 45° apart. Arrangements were made to support this disk at different heights above the crystal. Then at each 1-cm vertical interval from 1



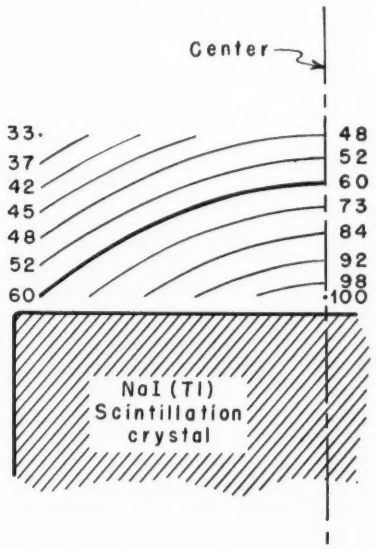


Fig. 1. (Left) Diagram of counting efficiency over scintillation crystal. For explanation, see text.

Fig. 2. (Right) Isosensitivity curves over scintillation crystal. Heavy line indicates optimal configuration for construction of counting dome.

to 10 cm, a point source of Cr^{51} was counted at the center of the disk and at each intersection of the radial and concentric lines. For this purpose, differential counting was utilized, the voltage window overlying the 0.32 mev photopeak of Cr^{51}.

Of course it was important that the count rate be highly accurate and that it be corrected for background and decay when necessary. Also, it was necessary to make determinations along each marked radius to ensure that the crystal's isosensitivity curves were radially symmetrical. A preliminary graph was made for the plane at each 1-cm vertical interval to express the counts at the etched intersections as percentages of the count at the center of the lowest plane. Since these indicated the radial symmetry was fairly exact (within 0.5 per cent), a plot was made of the counts along a single vertical radial plane (Fig. 2) and lines of equal counting rates (isosensitivity) were connected.

To be selected from these data was the optimal curve to use as a pattern for the upper surface of a hollow lucite isosensitivity dome. Which curve should one choose? That nearest the crystal—the lowest curve possible—would maximize the counts; but the flattest and widest would serve most conveniently for spreading the halved sanitary napkin. The curve drawn in the heavy line in Figure 2 was considered the best. Luckily the former curve proved to be sufficiently flat to serve as a counting surface.

When the foregoing steps had been completed, detailed counts were made at linear intervals of about 4 mm along the selected curve, and the exact positions of the points of equal count were plotted on graph paper. This graph was used as a cross-sectional blueprint for the fabrication of the counting dome. The thick-

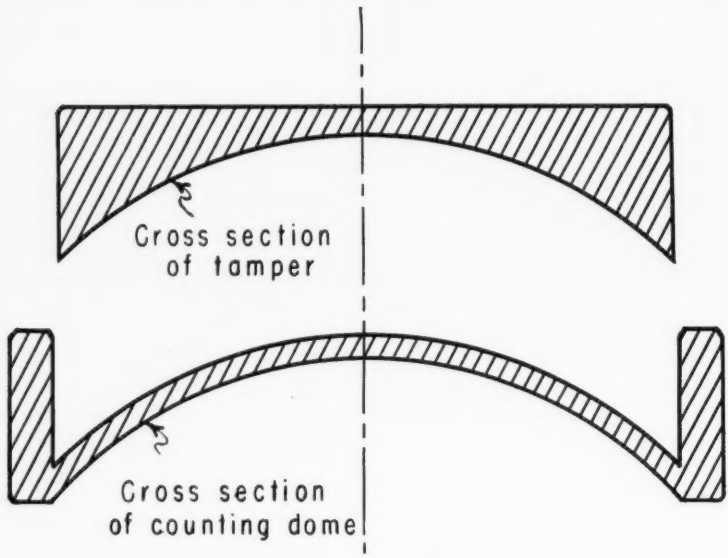


Fig. 3. Working diagram of cross-section of isosensitivity counting dome. The configuration of the counting surface was determined from the isosensitivity curve derived in figure 2.

Fig. 4. Photographs of finished lucite dome and tamper: *a*, assembled and *b*, apart.

ness of this dome was minimized to avoid attenuation of the counting rate. Since a flat curve of isosensitivity is not possible and since the pads are usually thick and sometimes stiff, they must be compressed to make a thin layer fitting the convexity of the dome. For this compressing, a concave tamper (or cover) is required. Originally we considered lead as a material for this tamper, but we found that one made of lucite is much easier to handle. Spring latching to the base may be worth while.

It is convenient for the dome to have a circumferential rim approximately 2 cm high and 0.5 cm thick so that the cover can fit easily into it. It is also convenient to fashion some sort of handle on the cover. Figures 3 and 4 show our final plan and its realization.

METHOD OF USE

Counting the Pads.—Since menstrual pads are oblong, the crystals are round, some handling of the pads is inevitable. They are cut across once, making two approximate squares which are counted separately.

We have insisted that the patient be consistent in the type of pad used during the period. Patients undergoing this kind of investigation almost always use the most absorbent size.

For a counting standard, we use a half pad of the same type used by the patient onto which 10 ml of peripheral venous blood has been spread with a volumetric pipette.

The Course of the Test.—Shortly before the patient expects her period to begin, her blood is labeled with approximately 150 μc of Cr^{51}. She is instructed to save every pad, to try to save every clot (voiding through a strainer of fine mesh may help), and to return to the laboratory when her period begins.

At this visit, 10 ml of venous blood is withdrawn and pipetted onto half of a clean pad. This pad is wrapped in saran wrap for use as a counting standard. (The saran covering allows the pads to be handled with less offense and prevents

TABLE 1

EXPERIMENTAL CHECK ON ACCURACY OF MEASUREMENT WITH COUNTING DOME

Quantity of blood, ml.	*Net cps (average of 3 100^{11} counts*)*	*Net cps/ml. blood*	*d*	d^2
1	104.15	104.15	−0.74	0.55
2	207.48	103.74	−1.15	1.32
4	421.73	105.43	0.54	0.29
6	627.95	104.66	−0.23	0.05
8	848.22	106.03	1.14	1.30
10	1053.13	105.31	0.42	0.18
	Mean	104.89	Total	3.69

$$\sqrt{\frac{3.69}{5}} = \sqrt{0.74} = 0.86$$

2 S.D. = 1.72 = 1.6 per cent of mean value

*Duration selected to reduce counting error to less than 0.5 per cent.

drying of the blood and subsequent stiffening of the pad so that it can be molded to the shape of the counting dome more readily.)

The patient is instructed to flatten out each used pad (tabs folded back) and place on it any clots she could collect in the strainer, to wrap it carefully in saran wrap, and to attach the date with Scotch tape. She is supplied with enough paper bags in which to collect the pads and asked to turn all of them in to the laboratory at the end of the period, at which time again 10 ml of venous blood is withdrawn and pipetted onto another half pad for the second standard.

Each used pad is then cut in half through its saran wrapping, and ends or corners containing no blood are trimmed away.

Now each standard half pad is placed, bloody side down, in the counting dome (which has been lined with another layer of saran), and pressed down to a constant thickness with the lucite cover. Three 100-second counts are taken, averaged, corrected for background, and divided by 10 to obtain the net counts per second per milliliter of blood at the beginning and at the end of the period. These values are plotted against the day of the period they represent and connected across. The standard counts per second per milliliter of blood on the intervening days are read off this graph. Each half pad actually used is then placed on the lucite counting dome and flattened with the tamper. The net counts per second per pad are determined. This figure is divided by the counts per second per milliliter of the peripheral venous blood of the same date (as read from the prepared chart), yielding the number of milliliters of blood contained on each half pad. These figures may be totaled per whole pad, per hour, per day, or per total period. We have found the total blood loss per day and per period to be the most interesting figures.

CHECKS AND RESULTS

In order to determine the accuracy of the method we pipetted varying quantities of Cr^{51}-labeled blood as unevenly as possible onto half pads and countered them on the dome. In this short series, two standard deviations equaled 1.5 per cent of the mean (Table 1).

Onto a small portion of pad (approximately 2 by 2 cm) we pipetted 1.0 ml of Cr^{51}-labeled blood. Counting at 10 different sites on the dome gave an 0.8 per cent error of radioactivity.

Among 12 subjects without anemia the mean total blood loss per menstrual period was 27 ml, the range being 6 to 50 ml. Among 10 patients having mild hypochromic iron-deficient anemia, the total loss per period ranged from 103 to 341 ml.

SUMMARY

A description has been given of a simple, accurate technic for the quantitation of menstrual blood loss, involving the determination of a three-dimensional isosensitivity curve and the fashioning of a lucite dome with cover to fit these specifications. Ten normal subjects lost no more than 50 ml each per menstrual period.

ACKNOWLEDGEMENT

With the technical assistance of Mitsue Y. Yamaguchi, M.S., M.T. (A.S.C.P.)

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Automatic Contour Myelography in Infants

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In the past, radioactive myelography has been limited in its application by lack of flexibility in the design of the detecting system and the poor cooperation on the part of the patient. The methods used by Bauer and Yuhl[1] and Perryman et al[2] were adequate for static measurements of radioactivity within the subarachnoidal space. However, when dynamic flow measurements were desirable, a more flexible system was needed to survey the activity. The inflexibility of design was eliminated with the construction of an automatic servo controlled contour scanner which had the usual scanning movements plus the incorporation of the unit in a tilt table.[3] In addition to this, the scanner was provided with a servo controlled contour sensing element to maintain constant geometry to an irregular curving surface. The usual problems of radioactive myelography are magnified considerably when infants are the subject of investigation. Adults can be persuaded to lie quietly beneath the scanner, but infants present as a moving target. When the usual scanning procedures are used, babies yielded uniformly poor pictures which could not be interpreted.

Recently we have applied the automatic contour scanner to the problem of producing a rapid picture of spinal subarachnoidal block.[4] The technique has been extended now to uncooperative infants. The contrast material, radioactivated human serum albumin, has been used for several years within the ventriculosubarachnoidal system and has produced only one minor reaction which could be traced to the material itself.[4,5] Therefore, we did not hesitate to use the material when young infants presented themselves with spinal cord lesions not suitable for the routine pantopaque myelography techniques. The automatic scan has been found to be an accurate test of the patency of the subarachnoidal space.

METHOD

The infant is placed on its side and a lumbar spinal tap is performed at an appropriate position. After the withdrawal of about 2 cc of spinal fluid, an

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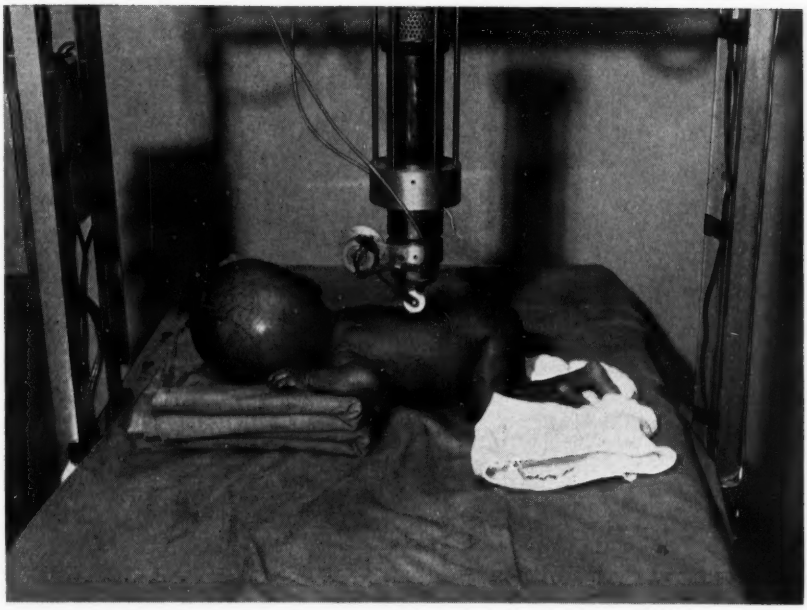

Fig. 1. The baby lies in a transverse position beneath the scanning head. The scanner follows along the saggital plane.

equal volume of radioactive albumin containing 100 uC of activity is introduced. The needle is withdrawn and the baby is then held in an upright position for 2-3 minutes. The child is then placed in a suitable dependent transverse position beneath the scanner (Fig. 1). The scanner is adjusted to travel at a speed of 0.5 cm/second from the sacrum to the occiput along the saggital plane. A suitable trial is made, the scale is adjusted, and the scanner activated. It is necessary to have a clinical neurosurgical evaluation of the level of the lesion so that the infant may be tilted to the proper angle on the table. This is done to be sure the material has come to rest at the level of the subarachnoidal block. As the machine is activated, the special following mechanism rides along the saggital plane of the infant. This area corresponds to the midline along the posterior spinous processes. The detector is coupled to a special sensing element which consists of a "selsyn" or synchro which has a plastic wheel attached to its rotor by a shaft (Fig. 2). This phase detection device is electrically connected to a phase sensitive amplifier. Slight changes in contour are reflected in motions of the rotor which in turn actuate the servo system. The system drives the detector to a predetermined position above the constantly changing contour of the spinal area. This type of mechanism permits the maintenance of a normal geometry and complete safety of the mechanism through constantly changing contours. One pass of the machine is sufficient to obtain a record of activity in the subarachnoidal space between sacrum and occiput. If an aural signal is available, one may readily note a change in activity near the block. The record itself is printed out on a

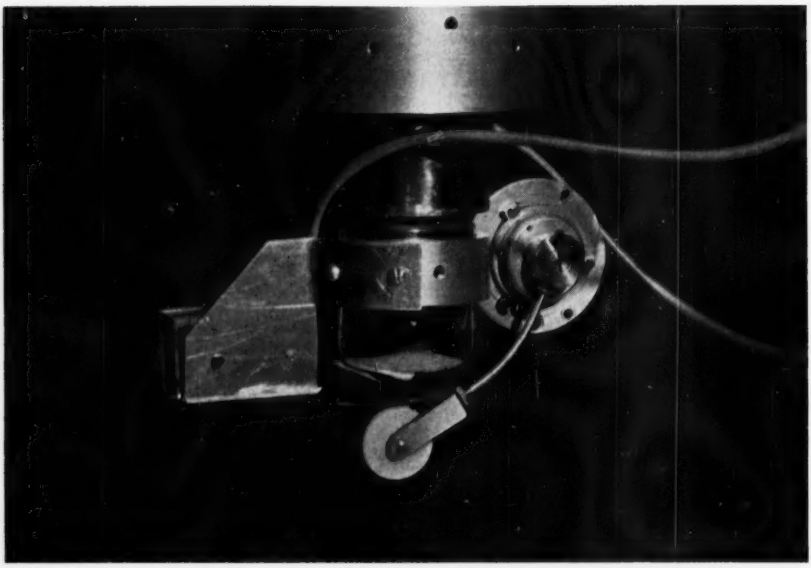

Fig. 2. View of the contour sensing element. The small microswitch is part of the fail safe sensing element. (By permission from Contour Scanner for Myelography, Bell, R. L. and Hertsch, G. J.: *Int. J. of Applied Rad. & Isotopes*, Nov. 1959, 7: pp. 19, Pergamon Press Inc.)

servo x–Y plotter (Fig. 3). With this single pass one may obtain a saggital radioactive myelogram. If one desires, one may mark the areas of the scan on the child and later leave these marks to be included on the x-ray films in order to compare the two records.

RESULTS

Baby R.B. KCH #31310, a three-months old girl, was admitted to the hospital on December 30, 1958 because of weakness in both legs. There had been no history of birth trauma but weakness had been noted in the legs shortly after birth. A neurological examination disclosed slight motion in the left lower extremity but there was no motion in the right lower extremity. Reflexes were not obtained on the right and were hypoactive on the left. An automatic scintiscan was performed and demonstrated complete subarachnoidal block corresponding to the level of the first lumbar vertebra (Fig. 4). The tumor, a neuroblastoma, extended from Lumbar 1 to Lumbar 4 and was attached on the right side. The greatest compression of the subarachnoidal space occurred at Lumbar 1-2 area. The slight disagreement in the scintiscan occurred because of the effect of tissue scatter and the limitation of resolution of the collimator and probe. The tumor was removed and the child was sent for radiation, following which she was returned home for further care. In this instance a complete subarachnoidal block was delineated, a nonabsorbable opaque material was not required for diagnosis,

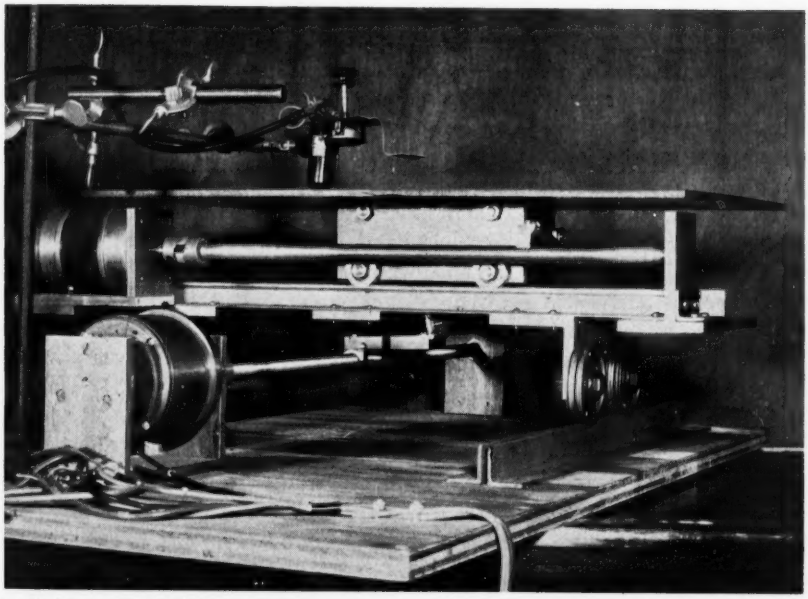

Fig. 3. Servo x—Y Plotter. (By permission from Contour Scanner for Myelography, Bell, R. L. and Hertsch, G. J.: *Int. J. of Applied Rad. & Isotopes*, Nov. 1959, 7: pp. 19, Pergamon Press Inc.)

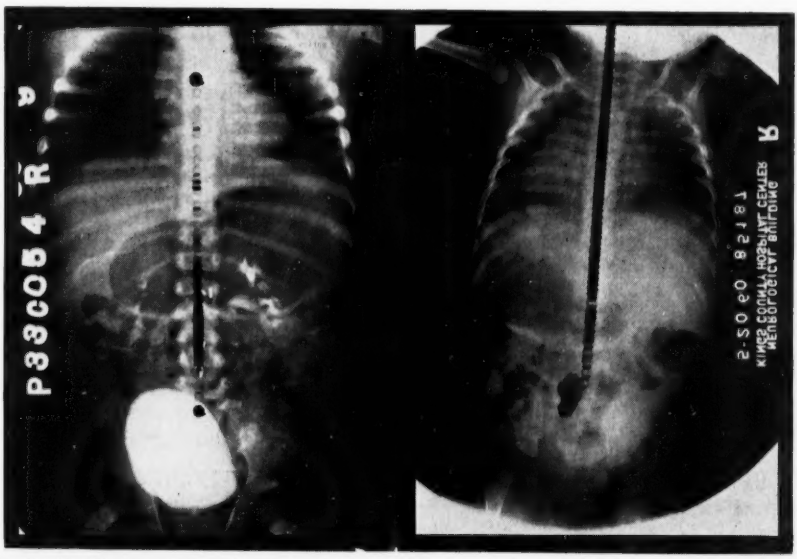

Fig. 4. (Left) Superimposed scan matched with x-ray of spine. The radioactivity is blocked at the L1-L2 level and cannot pass upwards.

Fig. 5. (Right) Superimposed scan matched with x-ray of the spine. The radioactivity is blocked at the Lumbar 3 level but is able to move upwards toward the head.

and the procedure was quickly accomplished. Without the recorder, hand scanning would not have given as adequate an evaluation.

S. H. KCH #6331, a seven-day old female, was born on Feburary 1, 1960 and was referred for evaluation of a lumbar myelomeningocele on February 8, 1960. It was also noted that there was progressive head enlargement. A neurological examination disclosed a lumbo-sacral myelomeningocele, 3.5-4 cm in diameter, overlying the lower lumbar and adjacent upper sacral area. The mass was covered with embryonal skin. There was no motion in the legs but there was slight flexion of the thighs on the pelvis. Painful stimulation could not be detected below the level of the knees. The anus was patulous. Reflexes were not obtained in the lower extremities. A ventricular-sinus shunt was performed on April 13, 1960 because of progressive head enlargement. The shunt functioned well for two weeks following which the head again enlarged. The shunt was obviously non-functioning. A radioactive myelogram was performed (Fig. 5). The area below L-3 at the upper border of the lumbo-sacral mass was found to have a decreased count rate and to exhibit subarachnoidal block. This is an instance in which a congenital defect coupled with adhesions produced a block in the subarachnoidal pathway. The material was quite free to flow cephalad but not distal in the region of the meningocele. The block was demonstrated subsequently at the time of repair of the meningocele and was at the L-3 bony level. In this instance again the test was rapid, accurate, and a picture of the extent of the subarachnoidal space was obtained without the use of an opaque, non-absorbable contrast medium.

SUMMARY

The saggital radioactive myelogram has been used as an aid to the diagnosis of the level of spinal subarachnoidal block in ten small infants. Among those who were examined by this technique were patients having subarachnoidal blocks for the following reasons: lumbosacral myelomeningocele (5 patients), neuroblastoma (2 patients), congenital sacral sinus tract (1 patient), epidural granuloma (1 patient), and diastomyelia (1 patient). The use of radioactive albumin within the spinal subarachnoidal space is safe and, coupled with an automatic contour scanning device, produces pictures rapidly. The material is absorbable. The only limitation of the method is the inability to detect very small encroachments on the subarachnoidal space. Two infants are presented to show the possibility of use of the method to aid in the diagnosis of subarachnoidal blocks produced by either tumors or congenital defects.

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JOURNAL OF NUCLEAR MEDICINE 3:293, 1962

Some Late Effects of Radiostrontium in RF Male Mice[1]

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Oak Ridge

INTRODUCTION

There is considerable interest in the potentially leukemogenic action of internally deposited radioactive strontium. Effects of radiostrontium on the incidence of various tumors have been reported in laboratory mice (1-5) and rats (6, 7). Since the induction of myeloid leukemia, a disease conspicuous among irradiated human beings and presumably related to irradiation of the bone marrow, has been extensively studied in the RF mouse under varying conditions of external and internal irradiation (8-11), it was considered of interest to study the effects of radioactive strontium in this test animal.

MATERIALS AND METHODS

RF/UP male mice were divided into five groups (Table 1). Since the presence of nonirradiated myelopoietic cells seems to inhibit myeloid leukemogenesis (11), splenectomy was performed on one group of mice to remove the extensive extra-medullary myelopoietic elements normally present in the spleen, thus leaving myeloid tissue predominantly subject to irradiation by the radiostrontium in bone. Radiostrontium was injected intravenously at 10 weeks of age, and groups undergoing splenectomy or sham splenectomy were operated on 4 weeks prior to injection. The animals were caged in groups of 8-10, with free access to food and water. At death a necropsy was performed on each mouse, and unless tissues were too decomposed, histologic sections were prepared (approximately 25 per cent of each group). In rare instances, owing to cannibalism or decomposition, no gross diagnosis was possible. The diagnosis of thymic lymphoma was made at necropsy when there was considerable enlargement of the thymus, with or without lymphomatous infiltration in other areas. Histologically, this neoplasm was characteristically a lymphosarcoma. The diagnosis of myeloid leukemia was made grossly when there was marked non-nodular enlargement and pallor of the spleen, enlargement of the liver, and relatively little or no enlargement of lymph nodes.

[1]Work done at the Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, operated by Union Carbide Corporation for the United States Atomic Energy Commission.

TABLE 1. MEAN SURVIVAL TIME AND MAJOR LESIONS IN RF MALE MICE RECEIVING Sr^{89} OR Sr^{90}

Group	No. of mice	Isotope injected (μc/g)	Mean survival time (months)	Neoplasm (per cent)							
				Reticular tissue			Lung	Liver	Bone		Total[c]
				Thymic	Myeloid	Other			Malignant	Benign	
I	51	0.2 Sr^{90}	18.88	17	0	48	20	2.1	4.2	2.1	81
Splenectomy			(±0.67)[a]								
II	57	0.2 Sr^{90}	17.70	13	5.6	48	13	0	0	3.7	72
Sham splenectomy			(±0.67)								
III	75	0.51 Sr^{89}	19.15 (±0.46)	5.3	0	78	12	0	0	1.3	84
IV	75	0.04 Sr^{90}	17.65 (±0.57)	5.3	0	74	5.3	0	1.3	1.3	80
V	67	0	19.75	1.5	8	35	21	1.5	0[b]	0[b]	61
Uninjected control			(±0.48)								

[a] Figures in parentheses indicate ± one standard error.
[b] This group was not examined roentgenographically.
[c] Per cent of animals with one or more neoplasm.

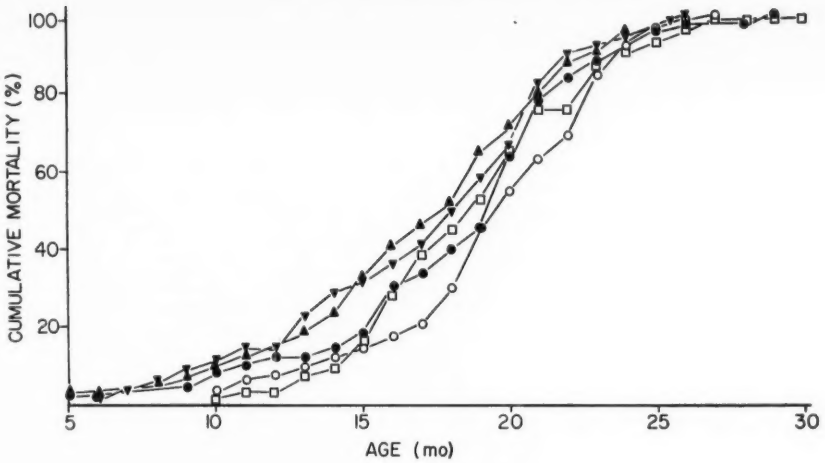

Figure 1.

Other gross and microscopic features of the disease have been described elsewhere (8). All other reticular neoplasms were lumped in a heterogeneous group, the principal subgroups of which were characterized grossly by: (a) generalized massive enlargement of lymph nodes, with or without nodular liver and spleen involvement, and (b) marked involvement of abdominal lymph nodes and kidneys, often with nodular enlargement of liver and spleen (those examined histologically were usually reticulum cell sarcomas). Post-mortem whole-body roentgenograms were prepared for approximately 90 per cent of the animals in Groups I-IV, and the previously undetected bone lesions thereby found were examined histologically. A group of 17 normal, 17-20 month old RF male mice, not set up originally as controls for this experiment, were likewise studied roentgenographically.

RESULTS

Table I lists the mean survival time and incidence of neoplasms in the different groups. There was a significant shortening of the mean survival time ($P = 0.01$) of animals of Group II (sham splenectomy and 0.2 μc Sr^{90}/g) and Group IV (0.04 μc Sr^{90}/g), but the life spans of the other injected groups did not differ significantly from those of the controls (Fig. 1).

Thymic lymphoma was more frequent in Group I (splenectomy and Sr^{90}, 0.2 μc/g) and tended to appear earlier in life in all injected groups (Fig. 2). The incidence of myeloid leukemia was unaffected. The other reticular tumors tended to appear later in life than thymic and myeloid types. They appeared earlier and in greater incidence in injected groups than in controls (Fig. 3).

The incidence of lung tumors was not increased in any injected group and was sigificantly lower ($P = 0.05$) in Group IV than in controls, possibly because Group IV had a somewhat shortened survival time. Other tumors of soft tissue were too few to be reliably correlated with the form of treatment.

[a] Figures in parentheses indicate ± one standard error.
[b] This group was not examined roentgenographically.
[c] Per cent of animals with one or more neoplasm.

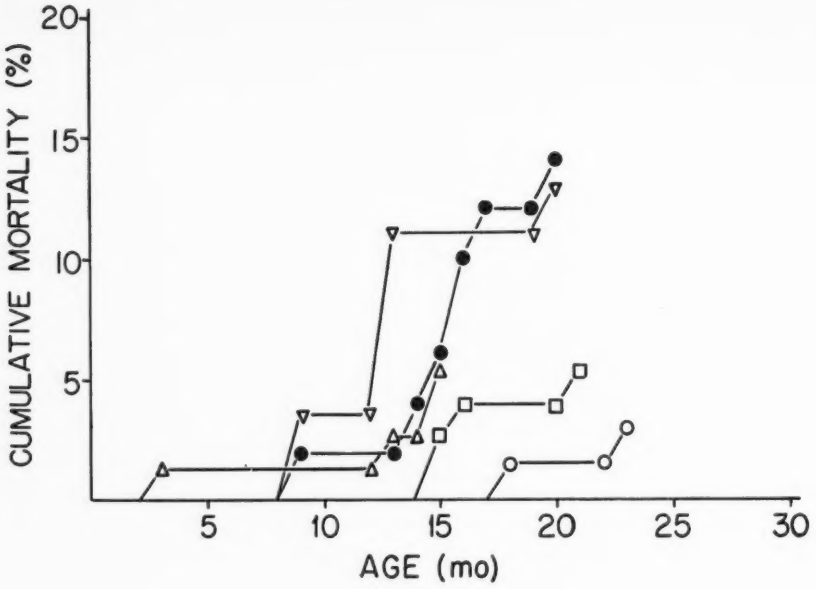

Figure 2.

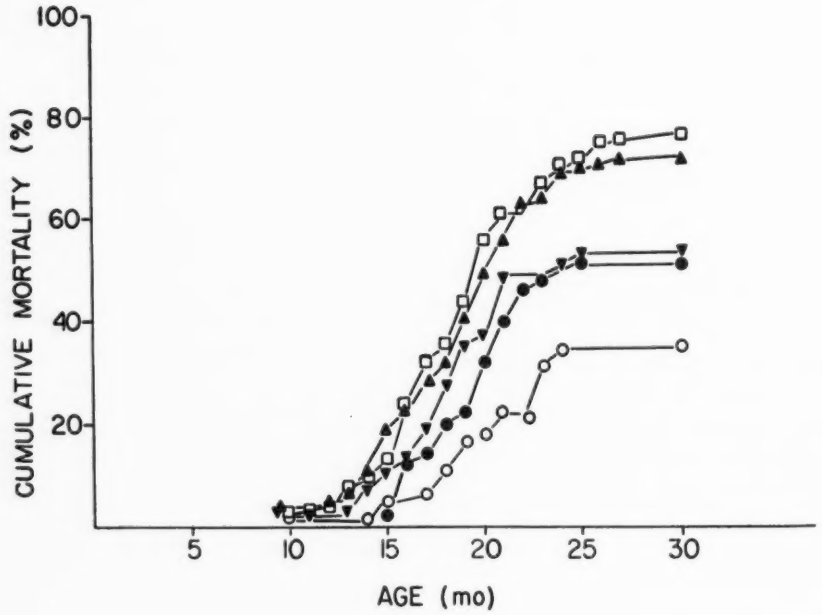

Figure 3.

Malignant bone tumors were found in Group I (osteosarcomas of left femur and right tibia) and in Group IV (osteosarcoma of sacrum). No osteomas were found at autopsy but five were discovered in subsequent skeletal roentgenograms as follows: Group I—left ilium, Group II—skull and sacrum, Group III—ilium, Group IV—right tibia. No bone tumors were noted in roentgenograms of 17 normal, aged, RF male mice. Post-mortem roentgenography and subsequent tissue sections of the treated groups revealed non-neoplastic bone lesions of various types in 2-10 per cent of the animals, including osteosclerosis, osteomyelitis, spinal hypertrophic arthritis, and congenital malformation of the thorax with deformed vertebrae, curvatures of the spine, and abnormal ribs. The same arthritic change was also noted in the group of 17 normal male RF mice.

Nephrosclerosis was noted in about 10 per cent of animals in all groups, including controls. Since, however, it was usually diagnosed only on histological examination, being poorly detected by gross observation, the percentage would have been considerably higher if all kidneys had been sectioned. Pneumonia and auricular thrombosis (present in 2-5 per cent of animals in most groups) and abscesses (present in 6-12 per cent of all groups, principally involving the liver, pelvis, and subcutaneous tissue) were the most common other diseases and bore no detectable relation to type of treatment.

DISCUSSION

The limited numbers of animals used in this experiment were given doses of radiostrontium based on the tumor-inducing doses of Sr^{90} reported by Finkel *et al.* (4, 5), and of Sr^{89} by Brues (1), Finkel *et al.* (2), and Kuzma and Zander (6). Our dose of 0.04 μc Sr^{90}/g was considered to be at or below the minimum dose for significant bone tumor induction.

The lower mean survival time in Groups II and IV was associated with earlier motrality from all recorded diseases. In view, however, of the lack of correlation between life span and dose of radioisotope, the observed effects will remain unexplained pending further study.

In the 285 animals receiving injections of Sr^{89} and Sr^{90}, three malignant bone tumors were found. This suggests that mice of the RF strain are, perhaps, more resistant to bone tumor induction by radiostrontium than strains previously used for such studies, since Finkel *et al.* (4) noted a 13.3 per cent incidence of malignant bone tumors with a dose of 0.2 μc Sr^{90}/g, a 5.6 per cent incidence with 0.044 μc Sr^{90}/g, and a 5 per cent incidence with 0.5 μc Sr^{89}/g (the latter two values were not significantly different from controls) in CF No. 1 female mice. Although our results and theirs cannot be directly compared because of strain and sex differences, our corresponding percentages were 2.1, 0, and 1.3 per cent, respectively. To what extent radiostrontium injection may have influenced the non-neoplastic bone lesions observed in 2-10 per cent of our animals cannot be assessed because of the small numbers of mice examined and the absence of similar roentgenographic studies in the controls.

The effects of radiostrontium on the incidence of leukemia were unexpected; i.e., it was not anticipated that the incidence of thymic lymphomas would be

increased and that of myeloid leukemias unaffected. Indeed, earlier observations suggested that partial-body irradiation was relatively less effective in the induction of thymic lymphomas than in the induction of myeloid leukemias, and irradiation at low dose rates was relatively ineffectual in lymphoma induction (see 11, 12). The induction of thymic lymphomas by Sr^{90} is, therefore, paradoxical. Although on first glance it seems surprising that the incidence of myeloid leukemia should not have been greatly increased in view of the high susceptibility of RF mice to induction of this disease by acute whole-body X-irradiation (11), the disease has not been induced with intravenously injected colloidal radiogold (9), or with chronic low-level γ-irradiation (A. C. Upton, unpublished data). The earlier appearance of leukemias and lymphomas, in general, among radiostrontium-injected groups agrees with the similar results of Finkel *et al.* (4, 13), who also noted a slight increase in the incidence of reticular neoplasms in their CF No. 1 mice given comparable doses of Sr^{90}.

Nephrosclerosis, pneumonia, auricular thrombosis, and abscesses were found in individuals of all groups. Since the numbers were small, no significant differences between groups were apparent for these diseases.

SUMMARY

Young adult RF male mice were injected intravenously with radioactive strontium as follows: Group I, 0.2 μc Sr^{90}/g after splenectory; Group II, 0.2 μc Sr^{90}/g after sham splenectomy; Group III, 0.51 μc Sr^{89}/g; Group IV, 0.04 μc Sr^{90}/g, and Group V, uninjected controls. After injection, the mice were observed until death, and effects on the life span and incidence of neoplastic and nonneoplastic diseases were studied. A dose of 0.2 μc Sr^{90}/g, with or without splenectomy, increased the incidence of thymic lymphosarcoma but did not detectably alter the incidence of myeloid leukemia. Other leukemias and lymphomas were also increased in number and occurred earlier. Two malignant bone tumors were found in 102 animals receiving 0.2 μc Sr^{90}/g, and one in 75 animals receiving 0.04 μc Sr^{90}/g, while none were noted in controls or in animals receiving 0.51 μc Sr^{89}/g. Effects on the life span were variable and of equivocal biological significance.

ACKNOWLEDGMENT

We are indebted to Mrs. F. F. Wolff and to Mrs. E. S. Ledford for technical assistance, to Mr. W. D. Gude and Mr. T. Mack for histological preparations, and to Dr. Miriam P. Finkel of Argonne National Laboratory for the preparation and examination of the roentgenograms and for helpful advice throughout the study.

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JOURNAL OF NUCLEAR MEDICINE 3:300, 1962

Comparative Counting Efficiencies of Co^{57} B_{12} and Co^{58} B_{12} For Three Counting Systems Using Two Detectors[1]

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Clinical investigations in our department using radioactive Co^{57} tagged vitamin B_{12}[3] and radioactive Co^{58} tagged vitamin B_{12}[1] (1) offered an ideal opportunity to study Co^{57} and Co^{58} from the counting point of view.

METHOD

For these studies, a Baird-Atomic Single Channel Gamma Ray Spectrometer that could be coupled individually to two different well type scintillation detectors was used for three different counting systems (Fig. 1).

The three different counting systems made available by the use of two well type scintillation dectectors were:

(1) A 2″ × 2″ NaI (T1) activated crystal with a 1⅛″ diameter well for large counting tubes. This well exactly encloses a 13 ml volume. The detector for this system is surrounded by lead 2¼″ thick on the sides and 1⅝″ thick at the top except at the 1⅛″ diameter opening for the large counting tube.

(2) A 1¾″ × 2″ NaI (T1) activated crystal with a ⅜″ diameter well for small counting tubes. This well will exactly enclose a 6 ml volume.

The detector for this system is surrounded by specially constructed lead shielding. It is 2⅝″ thick on the sides. The top of the lead shield has an overall diameter of 8½″ which is separated into two concentric circles of lead thickness. The lead thickness of the inner 4″ diameter circle is 1½″ thick. It is used for system 3. The lead thickness of the outer circle is 3″. The lead shielding top can be opened and closed (Fig. 2).

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1. From the Radioisotope Service, Veterans Administration Hospital, Albany, New York.
2. Siena College, Loudonville, New York.
3. Supplied through the kindness of Dr. Nathaniel S. Ritter, Merck, Sharp and Dohme Research Laboratories, Rahway, New Jersey.

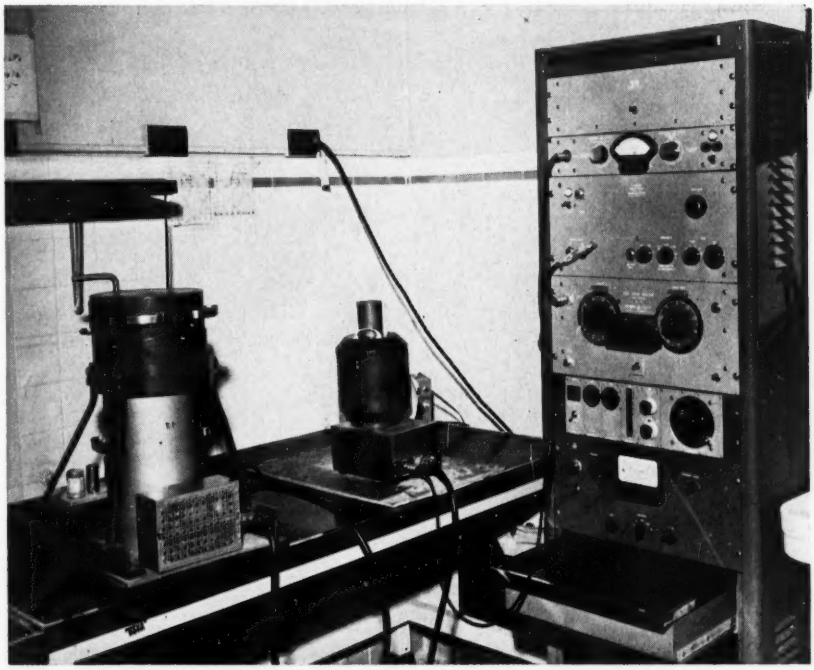

Fig. 1. Gamma Ray Spectrometer with two well type scintillation detectors.

(3) This system uses the same well with the same lead thickness as system 2. A calibrated glass beaker especially constructed to fit on and surrounding the small crystal is used. The beaker top fits up and into the 4″ diameter of 1½″ lead shield. The lead shield top can be closed to completely enclose the beaker. The capacity of this beaker is 600 ml (Fig. 3). Optimum operating points for integral counting (spectrometer window open) and differential counting (spectrometer window at 6.0 volts for Co^{57} and 7.4 volts for Co^{58}) were determined for the maximal value of S^2/B, where S is the corrected counts per minute and B is the background in counts/minute (2).

The data presented for differential counting of Co^{57} were obtained at the 0.123 Mev photo peak where the spectrum shows very little Compton scatter. The differential counting for Co^{58} was done at the 0.81 Mev photo peak where the spectrum shows a fair amount of Compton scatter. The counting loss due to scatter should be less for Co^{57} than for Co^{58}.

RESULTS

The number of counts detected as counts/min per microcurie by each system was determined (Table 1).

The counting efficiencies of Co^{57} and Co^{58} are shown as counts/min per microcurie. Co^{57} compared to Co^{58} is also expressed as a ratio (Co^{57}:Co^{58}).

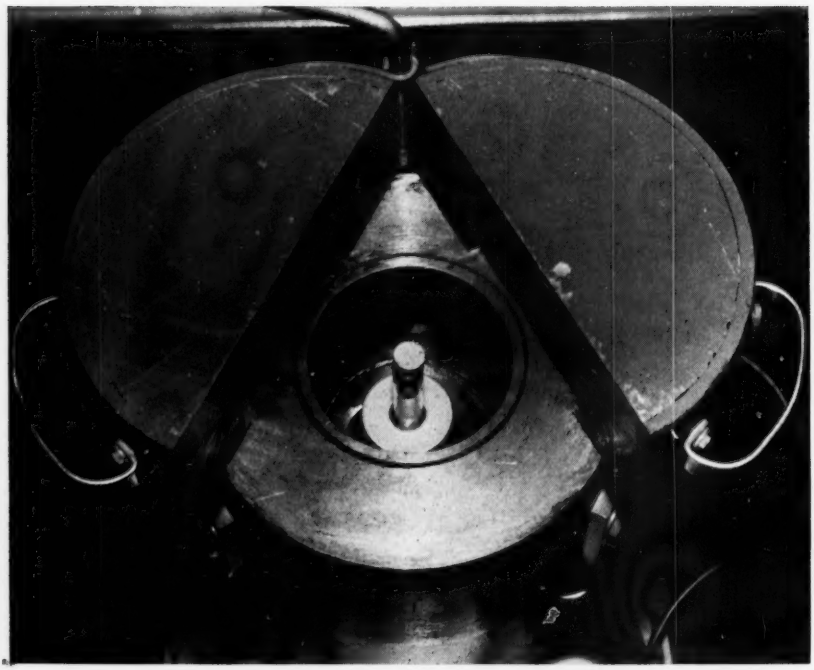

Fig. 2. Top view of system 2.

It can be seen that the counting rates from Co^{57} are from 4.8 to 7.6 times as great as those of Co^{58} when measured by differential and integral counting in the systems described above.

Table 1 also shows the background in counts/min for differential and integral counting of Co^{57} in system 1.

It can be shown that differential counting is decidedly superior to integral counting in respect to minimum counting time of samples with moderate counting rates and in deciding whether samples with low counting rates should be accepted as source counts or rejected as probable background variation.

Moderate Counting Rates. The data from Table 1 shows that a Co^{57} sample with an activity of 71.429×10^{-6} μc in a 10.0 ml volume would have a counting rate of 85 counts/min corrected and 115 counts/min with background counts by differential counting.

Using the optimum count chart of Loevinger (3), the γ value (where γ is the ratio of uncorrected counts/min to background counts/min) is roughly 4. If the sample percent error is to be 5, 10 minutes of counting time is required in differential counting. Table 1 shows the integral background to be 335 counts/min. The 10.0 ml, 71.429×10^{-6} μc sample counts/min corrected would be 102 and with background 437. The γ value is 1.3 and for the same sample percent error of 5 by Loevinger optimum count chart, the counting time is 32 minutes, a three-fold increase in counting time by integral counting.

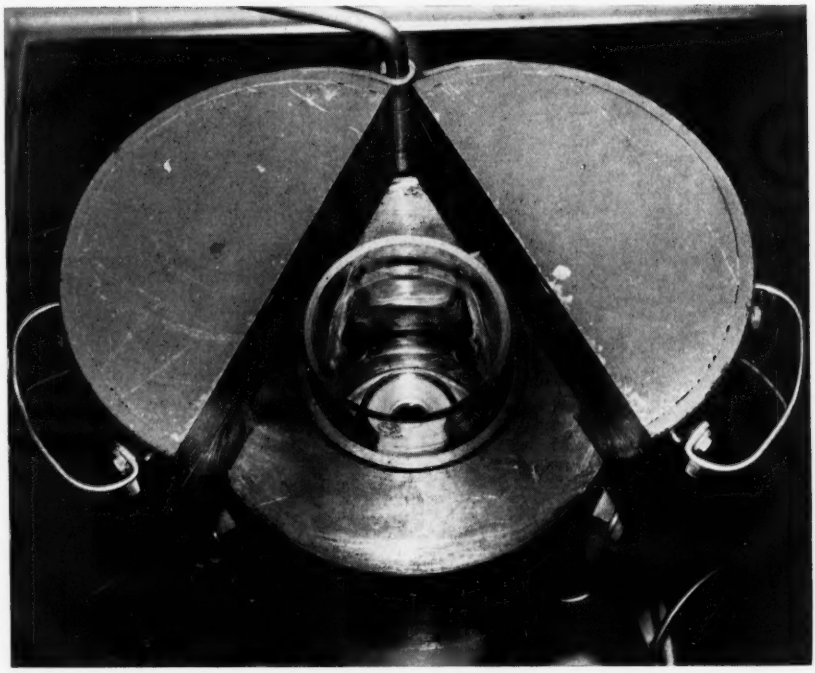

Fig. 3. Top view of system 3.

Low Counting Rates. Very often a low count rate specimen is of the greatest importance. The essential question—Is the count rate significantly different from background?—can be better answered with differential counting.

Jarrett (4) has shown that the formula $Y = K\ (Ns/ts + Nb/tb)^{1/2}$, where:

Y is the resulting error

K is a constant (1.96) for 0.95 error

Ns is sample count/min plus background

Ts is number of minutes sample was counted

Nb is count/min of background

Tb is number of minutes background was counted,

can be used to determine that a count is significantly different from background and be considered sample count if Y is less than the corrected counts/min. By the Jarrett formula, a sample with a counting rate of 4 counts/min corrected, following a period of one hour counting time for sample counting and one hour counting time for background, would be accepted as significantly different from background by differential counting but would be rejected as background by integral counting.

Smaller doses of Co^{57} will give the same or higher counting rate as larger doses of Co^{58} B_{12}. An identical dose of Co^{57} compared to Co^{58} will reduce the counting time considerably. The specimens with exceedingly low counts can be counted to a higher confidence level that was not reasonably possible before.

TABLE 1. EFFICIENCY OF Co^{57} AND Co^{58} AND RATIO OF Co^{57} TO Co^{58} USING THREE DIFFERENT COUNTING SYSTEMS

System		Co^{57} CPM/μc	Co^{58} CPM/μc	Ratio Co^{57}:Co^{58}
Differential				
1. Large Vial	8 ml.	1.24×10^6	1.75×10^5	6.5
	10 ml.	1.19×10^6	1.60×10^5	7.4
	12 ml.	1.11×10^6	1.48×10^5	7.5
Co^{57} Background = 30 cts. min.				
2. Small Vial	1 ml.	1.60×10^6	2.35×10^5	6.8
	3 ml.	1.52×10^6	2.30×10^5	6.6
	5 ml.	1.49×10^6	2.00×10^5	7.4
Co^{58} Background = 14 cts. min.				
3. Beaker	50 ml.	2.10×10^5	4.39×10^4	4.8
	100 ml.	2.01×10^5	4.03×10^4	5.0
	300 ml.	1.38×10^5	2.79×10^4	5.0
	600 ml.	8.74×10^4	1.75×10^4	5.0
Integral				
1. Large Vial	10 ml.	1.43×10^6	1.89×10^5	7.6
	12 ml.	1.33×10^6	1.77×10^5	7.5
Co^{57} Background = 335 cts. min.				
2. Small Vial	1 ml.	1.80×10^6	2.91×10^5	6.2
	5 ml.	1.58×10^6	2.40×10^5	6.6
Co^{58} Background = 90 cts. min.				
3. Beaker	100 ml.	2.00×10^5	4.31×10^4	4.6
	300 ml.	1.38×10^5	2.93×10^4	4.5
	600 ml.	8.60×10^4	1.79×10^4	4.8

SUMMARY

Co^{58} B_{12} and Co^{57} B_{12} were studied for relative efficiencies by integral and differential counting in three different systems.

Data were presented for the efficiencies of each system.

The advantage of differential counting was shown.

It was found, from the counting point of view, that Co^{57} is significantly superior.

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JOURNAL OF NUCLEAR MEDICINE 3:305, 1962

A Radioisotopic Approach to the Estimation of Mitral Valve Size[1]

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The most popular indirect method for the determination of mitral valve size today is the use of O_2 consumption and pulmonary wedge pressures employing the technique described by Gorlin. (1) In an effort to discover a simpler indirect method, 28 radioisotopic examinations were performed. This consisted of a preoperative and post-operative examination of 14 patients with the clinical diagnosis of "pure mitral stenosis (M.S.)". Curves were obtained from the passage of an intravenous bolus of I^{131} human serum albumin (10 to 20μc in less than .5 cc) through the heart with a collimated precordial scintillation probe. A similar probe also obtained curves over the abdomen at the umbilicus. The curves were recorded with a dual channel rectilinear recorder with a 0.5 second time constant at a paper speed of 12 inches per minute (Fig. 1).

The methods of curve analysis were:

1) Determination of the fractional cardiac output (Fco) as outlined by Shipley et. al.(2) The analysis of the precordial recording is as shown in the upper tracing of Figure 1. The cardiac output (CO) is measured as

$$CO = \frac{a}{d} \times \frac{BV}{t} \qquad (1)$$

Where BV is the blood volume, b is the average of the radioactivity levels over the heart during the bolus passage, a is the equilibrium blood level at 10 minutes,

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[3]Instructor of Medical Physics, Department of Radiology.

[4]Scholar in Radiological Research of the James Picker Foundation, Department of Radiology.

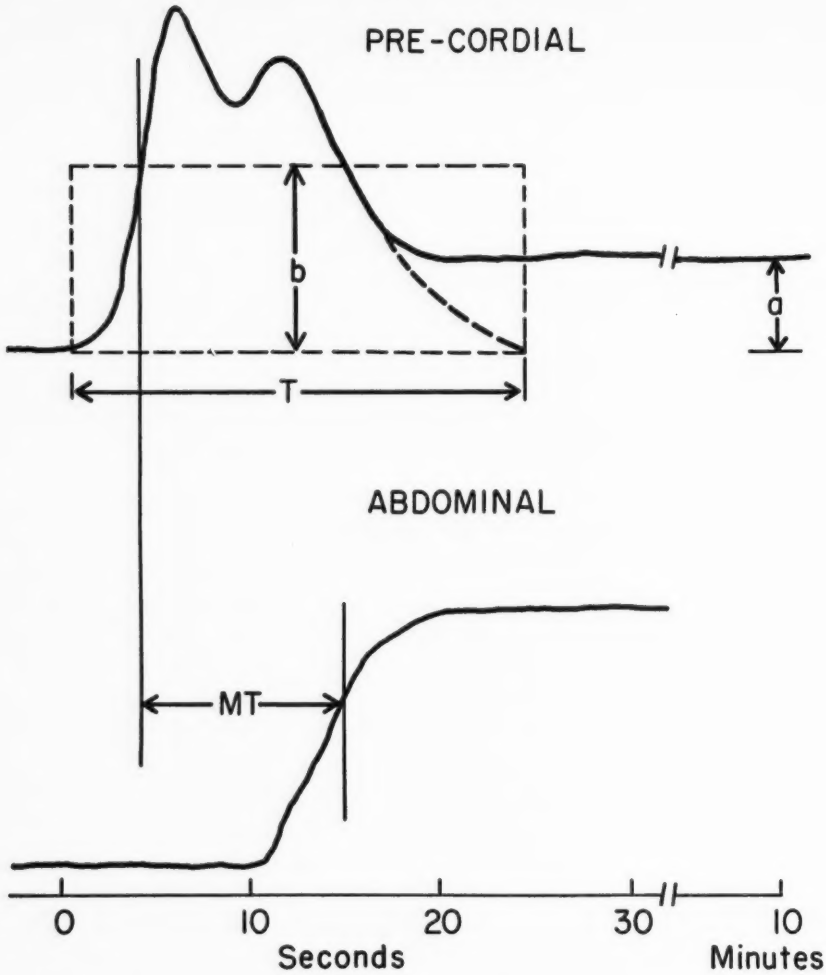

Fig. 1. Normal radiocardiogram with the descending limb extrapolated with a heavy broken line, the area of the heart curve illustrated with a thin broken line, and the measurements used in analysis labeled.

and t is the time in minutes for the passage of the bolus through the heart. If both sides of Eq (1) are divided by BV, the value Fco/min is obtained;

$$\text{Fco/min} = \frac{a}{b\ t} \quad (2)$$

where Fco/min is the fraction of the blood volume expelled from the heart per minute. If the fractional cardiac output per minute is divided by the pulse rate (P), the quantity obtained is the fractional stroke volume (Fco/P).

2) The mean transit time (MT) is the time interval between the mean appearances of the radioactive bolus in the heart and in the abdominal aorta. This is obtained by planimetry. This time is expressed as the number of ventricular systoles (beats) occurring in the interval (obtained from simultaneous electrocardiogram).

3) An integration of methods (1) and (2). In mitral stenosis the mean transit time (MT) is increased and the fractional cardiac output per beat (Fco/P) is decreased. Since these vary in opposite directions, the quotient (A) was also obtained:

$$A = \frac{MT}{Fco/P} \qquad (3)$$

At cardiotomy, the clinical diagnosis was confirmed in all cases and the cross-sectional area of the mitral valve opening estimated by the cardiac surgeon (in most cases by digital examination) before and after valvulotomy. The results were arbitrarily grouped into 3 ranges of valve sizes and are compared in Table 1 along with 23 non-rheumatic normals whose average age was 34.2 years. All parameters investigated demonstrated the ability to separate the severely stenotic

TABLE 1. TABLE OF ISOTOPIC PARAMETERS MEASURED IN PATIENTS WITH KNOWN MITRAL VALVE SIZE AND NORMALS. PROBABILITIES ARE INTERPOSED BETWEEN GROUPS INVOLVED.

Valve Size (cm^2)	*Fco/min.*	*Fco/P*	*MT*	*A*
Less than 1.5 $cm.^2$ (N = 9)	70 ± 17	0.80 ± 0.16	27.3 ± 3.6	31.2 ± 5.4
P*	0.003	<0.001	<0.001	<0.001
1.5–3.5 $cm.^2$ (N = 12)	117 ± 33	1.40 ± 0.35	18.3 ± 3.1	11.7 ± 2.2
P*	>0.50	0.25	0.04	0.02
greater than 3.5 $cm.^2$ (N = 7)	122 ± 36	1.61 ± 0.28	14.5 ± 4.3	8.7 ± 1.1
P*	>0.50	0.30	0.35	0.006
Normals (N = 23)	130 ± 34	1.75 ± 0.30	13.0 ± 3.2	7.4 ± 0.9

*The probability that the groups above and below the number are drawn from the same population (all probabilities less than 0.05 are considered indicative of two populations).

mitral valves from the less severely stenotic and normals. The quantity A was statistically the best separator of the arbitrary groups.

Congestive heart failure alone in the rheumatic or non-rheumatic increases the transit times and interferes with the valve size estimation by this method.

It was interesting to observe that reversion of atrial fibrillation to normal sinus rhythm by the use of quinidine sulfate resulted in a small but consistent decrease in transit time. Otherwise the parameters were consistent for the same patient in the same clinical state.

The increase in mean transit times and diminution in fractional cardiac output are not diagnostic of mitral valvular stenosis. Similar changes have been encountered in mitral insufficiency. Similar and more marked changes have been encountered with cor pulmonale.

SUMMARY AND CONCLUSIONS

1) Three methods of analysis of the radiocardiogram are described.
2) Their accuracy in estimation of mitral valve size was investigated. Normal valves are also presented.
3) All techniques can select the severely stenotic mitral valves (cross-sectional area less than 1.5 cm^2). Selection of less stenotic valves and normal valves from each other is less accurate.
4) If the clinical diagnosis of M.S. is certain, radioisotopes afford a simple method of estimating valve size.
5) This approach opens a new avenue to the objective evaluation of mitral surgery; and, possibly most important, to the diagnosis of re-stenosis of the mitral valve in the postoperative patient.

ACKNOWLEDGMENT

We wish to express our appreciation for the assistance of C. Glenn Sawyer, M.D., Associate Professor of Medicine, and Frank R. Johnston, M.D., Assistant Professor of Surgery.

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JOURNAL OF NUCLEAR MEDICINE 3:309, 1962

Observations on the Uptake of I-131-Triiodothyronine by Erythrocytes[1]

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INTRODUCTION

Considerable interest exists in the biochemical and clinical significance of the "uptake" of I-131-triiodothyronine (T-3) by erythrocytes, a practical laboratory test developed by Hamolsky[1,2,3]. This test has been shown to be very useful and of real clinical value by various investigators, among these Robbins[4], Schumacher and King[5], etc. [6,7] The physiological parameters measured by this T-3 uptake by red blood cells (T-3-RBC) have been subject to considerable investigation[8,9]. Some laboratories have become interested in determinations of the biochemical and physical-chemical limits of these tests[10,11,12,13]. In our laboratories this test has been found to be helpful in clinical diagnosis. The biochemical significance of this technique, the measurement of its useful limits, and efforts toward its simplification are here discussed.

EXPERIMENTAL

The laboratory conditions employed for each series of experiments are indicated in each table. The basic method of Hamolsky[3] was followed throughout the RBC "uptake" and washing of the RBC (where indicated) was done by allowing the red blood cells to stand for 10 minutes in the washing solution prior to centrifugation. Various commercial preparations of I-131-T-3 were used in this work. Each batch was assayed by descending paper chromatography with a 0.2 M ammonium acetate-ethanol solution.

In the first experiments the effects of varying erythrocyte mass were determined as shown in Table 1. The effect of various incubation temperatures was determined as shown in Table 2. The variations in incubation time were deter-

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1. All radioactive materials obtained under allocation of the U. S. Atomic Energy Commission.

2. Radioisotope Service, Veterans Administration Hospital, Biochem. Dept. U. of P. and Research Laboratory, Department of Radiology, Albert Einstein Medical Center, Southern Division, Philadelphia, Penna.

TABLE 1

EFFECT OF VARYING RBC MASS ON THE "UPTAKE" OF T-3*

*Packed volume of washed RBC** added to 1 ml of plasma*	*Recovered radioactivity† in the erythrocytes Counts ± 3%††*
0.3	142
0.5	152
0.7	150
0.9	157
1.1	153
1.5	160
2.0	150

*0.001 μg of 1-triiodothyronine-I-131 incubated at 37 C for 3 hrs. in closed Erlenmeyer flasks.

**Pooled washed erythrocytes from one donor.

†Samples done in quadruplicate and averaged; also corrected for geometry change due to volume.

††Estimated range from several similar experiments.

mined as shown in Table 3. The approximate amount of protein-bound I-131-T-3 found in the plasma after T-3 incubation was determined following precipitation with 5 per cent trichloracetic acid solution, and washing by centrifugation with a saturated solution of protein-bound I-131-T-3. Incubation of plasma in the presence or absence of RBC's was carried out. These results are in Table 4 and 5. Table 6 depicts results of the "T-3-RBC" uptake test when mixed erythrocytes of various species were used.

RESULTS AND DISCUSSION

Variations in RBC mass (under the experimental conditions employed) have been shown to have no appreciable effect on T-3 uptake (c.f. Table 1). This suggests that an ideal or simplified test would not require knowledge of percentage RBC mass. This points to the possible use of sera for a "similar" test. (The hematocrit is known to change in many conditions with no thyroid involvement—thus the test is affected by this correction). The great dependency on temperature and time of incubation (Table 2 and 3) for the T-3-RBC "uptake" suggests an absorption-desorption equilibrium typical of "Freundlich-isotherms" between the RBC's and the T-3 in solution. The approximate values for the protein-bound T-3 remaining in the plasma after incubation (Table 4) were obtained after 5 per cent TCA precipitation and suggests that *most* of the free or unbound T-3 in solution was available for RBC absorption and could have been absorbed. When plasma was incubated with an I-131-T-3 solution in the absence of RBC's, and the protein-bound T-3 precipitated with a 5 per cent TCA solution and the fractions assayed, it was observed that the percentage binding obtained after a few

TABLE 2

EFFECT OF TEMPERATURE ON THE UPTAKE OF T-3* BY ERYTHROCYTES**

Temperature ± .2 C	*Recovered radioactivity in CPM in the 0.4 ml packed-washed erythrocytes*† ±3%††
30	212
33	257
37	278
40	240
45	249
50	—

*0.04 μg of 1-triiodothyronine-I-131 incubated for 3 hrs. in closed Erlenmeyer flasks.
**Packed and washed erythrocytes from one donor.
†Samples done in quadruplicate and averaged: washed under same conditions.
††Estimated range from several similar experiments.

minutes' incubation showed no gross difference from that obtained after several hours of incubation. Thus for actual purposes it may be assumed that the protein-binding of T-3 under these conditions was well accomplished after a few minutes (Table 5). Thus we again confirm that the lengthy incubation required in the T-3-RBC Hamolsky test is for the establishment of the absorption-desorption equilibrium of the RBC's with all components in the mixture.

All commercial samples of I-131-T-3 tested contained some free I-131-iodide and had varying shelf-life for which no correction can be made unless a sample

TABLE 3

EFFECT OF INCUBATION TIME ON UPTAKE OF T-3* BY ERYTHROCYTES**

Time in hours	*Recovered radioactivity in CPM in erythryoctes*† ±3%††
0.5	132
1.0	215
1.5	242
2.0	253
2.5	258
3.1	270
3.5	264
4.0	268

*0.001 μg at 1-triiodothyronine-I-131 incubated at 37 C in closed Erlenmeyer flasks.
**Packed and washed aliquots from one donor.
†Samples done in quadruplicate and averaged washed the same way.
††Estimated range from several similar experiments.

TABLE 4

DISTRIBUTION OF T-3* AFTER INCUBATION (PROTEIN-BOUND AND IN RBC's)

Patient	*in RBC's***	*% Averaged radioactivity recovered in TCA precipitated plasma*†
a	12	87
b	8	90
c	18	80
d	10	92
e	17	80
f	16	79
g	9	93
h	10	87
i	22	71
j	4	98
k	14	81
l	17	88

*0.001 μg of 1-triiodothyronine-I-131.
**Duplicate runs incubated for 3 hrs. at 37 C in closed Erlenmeyer flasks and washed.
†Plasma and washings treated with 5% TCA solution and washed.

is preassayed prior to each use. The required lengthy incubation and to some extent the washings, liberate some free iodide from the materials; this could be corrected by iodide assay after the completed test. Table 6 confirms previous work[1] and shows the results obtained by the mixed use of plasma and red blood cells of various species and from blood of patients with different thyroid conditions. The approximately equal values obtained from the "mixed" plasma and RBC's may be interpreted as showing that no innate differences exist in the T-3

TABLE 5

EFFECT OF TIME INCUBATION ON THE PROTEIN-BINDING OF I-131-T-3 BY PLASMA

Time	*CPM Radioactivity recovered* * **
1 minute	198
5 minutes	195
15 minutes	210
30 minutes	190
60 minutes	185
120 minutes	187
180 minutes	198
240 minutes	182

*0.001 μg of I-131-1-triiodothyronine per ml plasma at 37 C.
**After 5% TCA solution and washed.

TABLE 6

EFFECTS OF "SPECIES" OF ERYTHROCYTES AND EFFECT OF HUMAN HYPER-, HYPO-, AND EUTHYROID'S ERYTHROCYTES ON T-3* "UPTAKE"** ON THE SAME PLASMA

Type of RBC's	*Averaged recovered radioactivity CPM in erythrocytes† ±3%††*
Sheep	230
Mouse	239
Rat	219
Rabbit	245
Human	
a. Same individual's as plasma's	237
b. A euthyroid	240
c. A hypothyroid	221
d. A hyperthyroid	219

*0.001 μg of 1-triiodothyronine-I-131

**Samples done in quadruplicate, incubated at 37 C for 3 hrs. in closed Erlenmeyer flasks with 1 ml. of plasma from one donor.

†Washed and packed RBC's 0.5 ml.

††Estimated range from several similar experiments.

absorption capacity or ability of the various red blood cells tested under these conditions.

All of the above observations may be interpreted to point to the need for the development of an *in vitro* test with all the advantages of the Hamolsky method but a) not temperature dependent, b) not requiring hematocrit correction, c) not with time-consuming absorption and washing equilibration, d) not needing a correction in total I-131-T-3 because of the presence of free I-131.

A chromatographic method is thus suggested as one capable of the separation of free I-131, protein-bound I-131-T-3 and free I-131-T-3 in sera. This method[14] would at the very least be a useful adjunct to the Hamolsky technique. The results obtainable from such a chromatographic method would give a ratio of protein-bound to total I-131-T-3 in the sera of the patient. Such a technique and other similar ones necessitate the analytical separation and assay of a very large percentage of the total radioactive material of the mixture (i.e. 80-100% of radioactivity employed to be assayed and compared to total). The absolute error in analytical assays involving separation and measurement of a large component (close to 100% of the total) is difficult to estimate and usually shows a greater error than analytical assays in which a small component of the mixture is to be separated and measured[15]. The Hamolsky method requiring assays of 10 to 20% of total radioactivity falls within this latter category. Yet, a simplified *in vitro* method would be a great asset for clinical evaluation of many thyroid conditions which are difficult to determine. See accompanying paper for a new chromatographic method[14].

SUMMARY

1. The Hamolsky "T-3-RBC" test was shown in all of our work to be very useful and practical although exacting.

2. Observations suggest great dependency on temperature, incubation time, and washing methodology for reproducibility.

3. Free I-131-iodide correction was necessary for greater accuracy.

4. The lengthy incubation used was found not to be required for protein binding of the I-131-T-3 in the plasma but needed for equilibration of "isothermal" absorption-desorption of free I-131-T-3 and other components and the RBC's.

5. A chromatographic technique capable of separating free I-131 iodide, bound and unbound I-131-T-3, is suggested and is discussed.

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Localization of Hydatid Liver Cysts with Colloidal Radiogold

International Atomic Energy Agency Scanning Program in Iraq[1]

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Los Angeles

INTRODUCTION

In Iraq, hydatid disease remains a medical problem. During the period 1955-1959, of 22,231 major surgical operations performed in the Republic Hospital in Baghdad, 435 of them were cases of hydatid disease. Such a prevalence was known to the famous Arab physician, Al Rhazes (AD 860-932), who described the cyst.

In the life cycle of the Taenia *Echinococcus granulosus* (1) the dog, jackal, and wolf are definitive hosts. The eggs are passed with the feces and transmitted to the intermediate host either through direct contact or indirectly by food contamination. The intermediate host can be man, sheep, or cattle. An increased incidence has been found in poor, crowded districts, where infected parts of slaughtered sheep are eaten by stray dogs.

The eggs hatch in the stomach of the intermediate host, liberating onchospheres, which penetrate the gut wall into the lymphatics or tributories of the portal vein. The majority are filtered first in the liver before spreading to the lungs and other organs. For this reason, 70 per cent of all cysts are seen in the liver.

Small cysts are usually symptomless. They grow slowly to a large size over several years, giving rise to a feeling of heaviness in the right hypochondrium,

1. This work was performed under a research contract with the International Atomic Energy Agency.

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Present Address: University of Sheffield, Sheffield, England.

4. Department of Surgery, Republic Hospital, Baghdad.

and occasionally pain. Some cysts become infected, producing the signs and symptoms of liver abscess. Rupture of the cyst may produce severe anaphylactic shock and the formation of secondary cysts in the peritoneal cavity. Rarely, the bile ducts are blocked, resulting in obstructive jaundice.

In an endemic area, the diagnosis of hydatid disease of the liver and the preoperative localization of the cysts are frequently quite well established upon clinical examination, which may reveal the presence of a cystic mass in the right hypochondrium or the epigastrium. Eosinophilia is usually present but has little diagnostic value where most patients harbor other helminthic infestations. The Casoni intradermal reaction is helpful but was found by one of us (Kh. Q.) to be negative in 26 out of 91 patients with hydatid disease confirmed at operation. False positive reactions are also known. Eight out of 100 Casonis done on normal medical students were positive. X-ray examination is seldom helpful in the diagnosis of hydatid cyst of the liver. Rarely may it show elevation of the dome of the diaphragm, areas of calcification in the cyst wall, or a deformity of the cholecystogram.

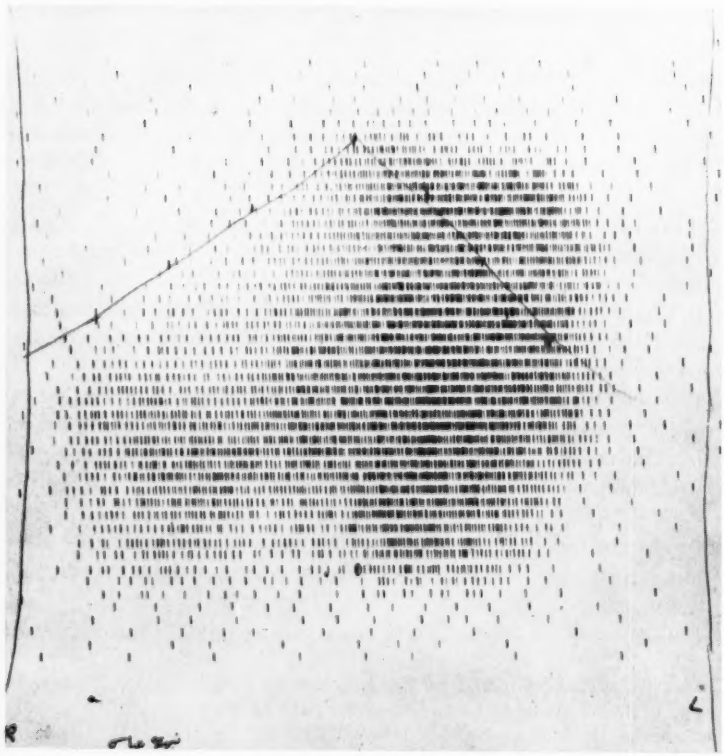

Fig. 1. Case study No. 1. Hydatid cyst in the right upper quadrant with gross displacement of functioning liver tissue.

Sheppard et al (2) first showed colloidal radiogold to be taken up by the Kupffer cells of the liver. This phenomenon was employed by Vetter, et al (3) for the measurement of liver blood flow by external counting. Liver scanning with radiogold, first reported by Stirret and associates (4), has been developed by von Renfer (5), Donato (6), and others. Liver scanning for hydatid cysts has been reported by Czerniak and associates. (7), (8)

EQUIPMENT

The authors employed an automatic scanner[1] provided with three inch scintillation detector, 61 aperture focussed collimator (9), and scaler-analyzer. Pulses from the scaler are supplied to a background subtractor[2] (10,11). This instrument incorporates a glow transfer tube and associated electronic circuit designed to produce clockwise transfers for pulses from the scaler. It also provides a pulse generator of variable repetition frequency, pulses from which produce counterclockwise transfers. This subtract frequency can be adjusted to cancel most of the background, improving contrast without erasing information.

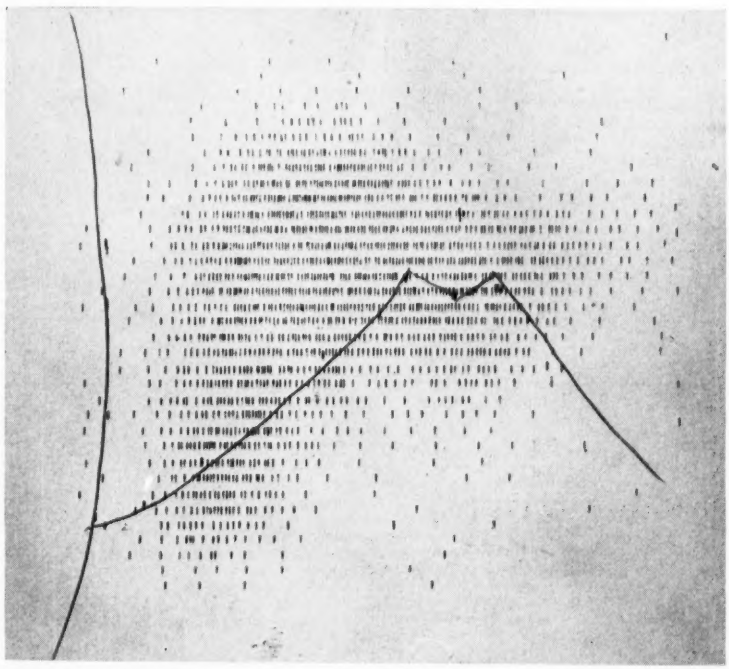

Fig. 2. Case study No. 2. Small hydatid cyst at the inferior border of the liver with slight deformity.

1. Nuclear-Chicago model 1700A.
2. "Contrast amplifier" formerly manufactured by R. C. Scientific Instrument Co., Playa del Rey, California.

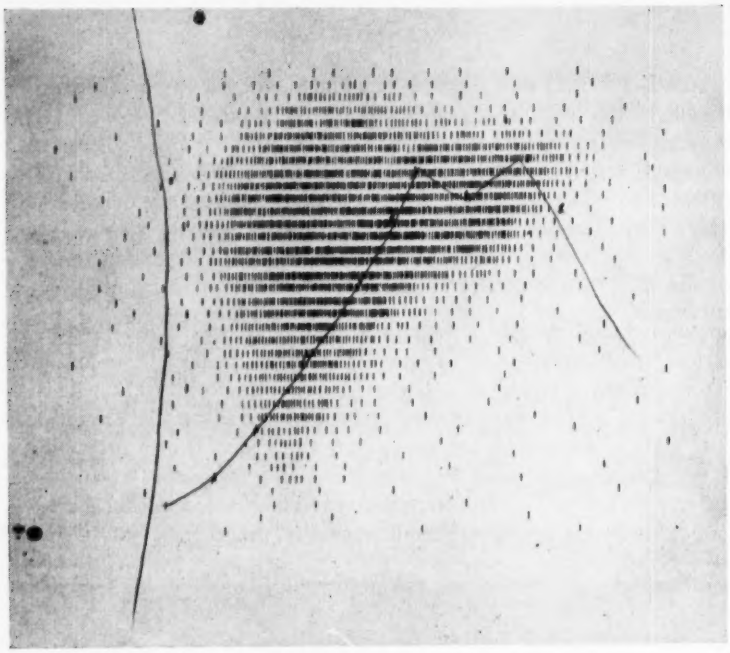

Fig. 3. Case study No. 3. Normal appearing scintigram of the liver in the presence of hydatid cyst of the lung.

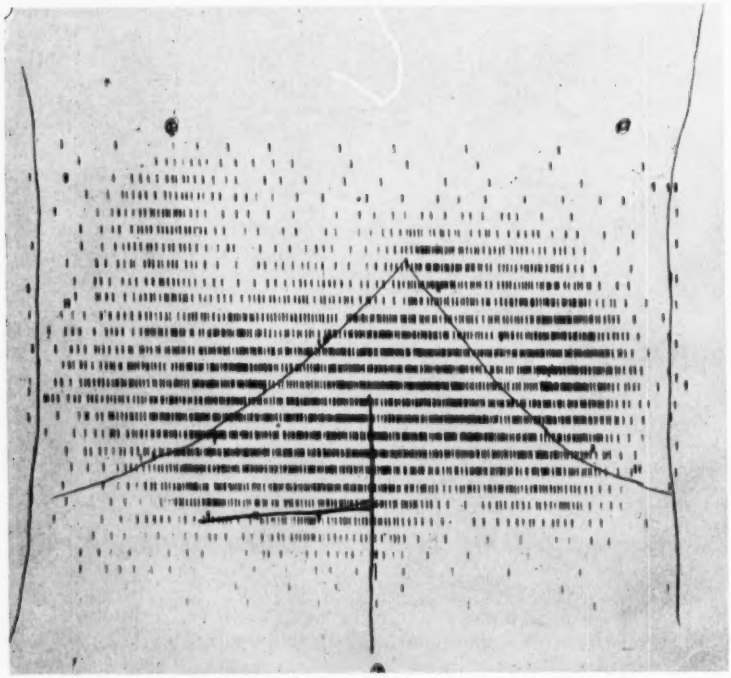

Fig. 4. Case study No. 4. Multiple hydatid cysts remaining from previous surgery.

PROCEDURE

Scanning is begun 30 minutes or more following intravenous injection of 500 microcuries colloidal radiogold. Scans are usually made in an anterior projection. The analyzer channel is adjusted to accept pulses in the range 36-46 volts, with amplifier gain and photomultiplier tube supply voltage adjusted to center the 0.41 Mev gamma photopeak into this channel. Pulses divided by a scale of two and supplied to the subtractor result in an overall counts-per-stroke factor of 20. A rapid scanning speed of 4 mm per second is usually required to complete the procedure within one hour.

CASE STUDIES

No. 1. B. A. female, 35 years. Complained of heaviness and pain in the right hypochondrium. On examination, the liver was felt 10 cm below the right costal margin. Casoni test was positive. W.B.C. differential count showed 9 per cent eosinophiles. Chest x-ray was negative. Liver scanning revealed a large void in

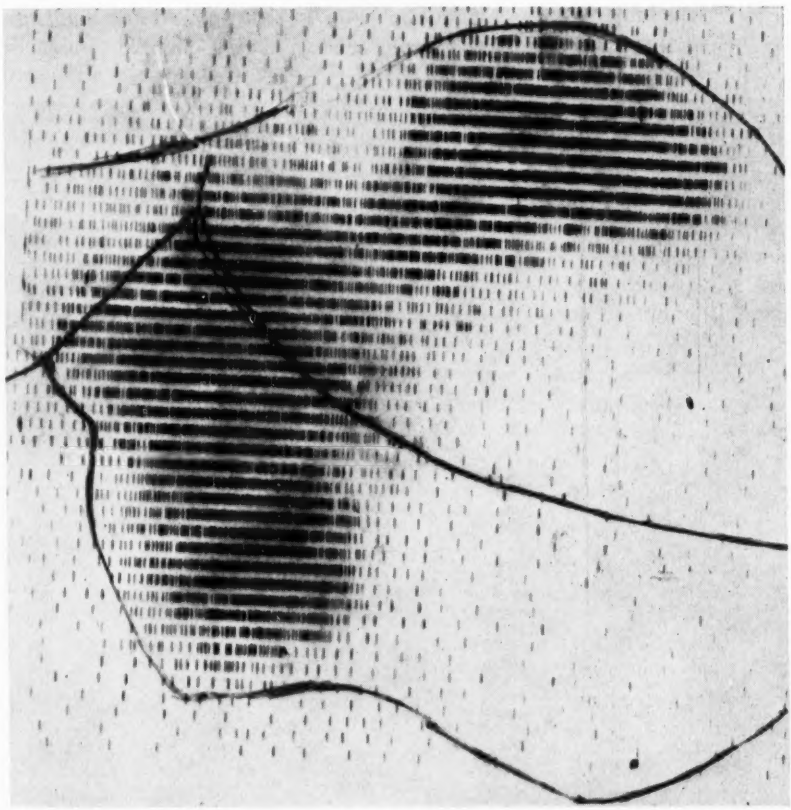

Fig. 5. Case study No. 5. Large palpable mass in the liver shown by scintigram to be normal liver tissue displaced by a large mass farther to the right. Hydatid cyst remaining from four surgical procedures.

the area of the liver with displacement of the functioning liver tissue downward and to the left (Fig. 1). On operation a large cyst containing approximately 1000 cc's hydatid fluid and daughter cysts was removed. Recovery was uneventful.

No. 2. N. F. female, 40 years. The patient complained of a mass in the right hypochondrium. On examination, a cystic mass about the size of an orange was felt. The casoni was negative. Scintigram revealed a deformity of the lower edge of the liver, not in itself conclusive, but consistent with the position of the mass (Fig. 2). At operation, an infected hydatid cyst was found, and approximately 150 cc's of purulent hydatid fluid was aspirated.

No. 3. K. S. male, 32 years. Admitted to the hospital with the diagnosis of hydatid cyst of the lung demonstrated on chest film. Casoni was positive. Scintigram revealed no evidence of abnormality in the liver. (Fig. 3). The chest lesion was removed surgically, and the patient recovered uneventfully.

No. 4. F. H. male, 20 years. The patient complained of heaviness in the right hypochondrium. The Casoni was positive. He had been previously operated upon for hydated cyst of the liver. Scintigram (Fig. 4) showed void areas still present and indicated the need for another exploration through a different approach.

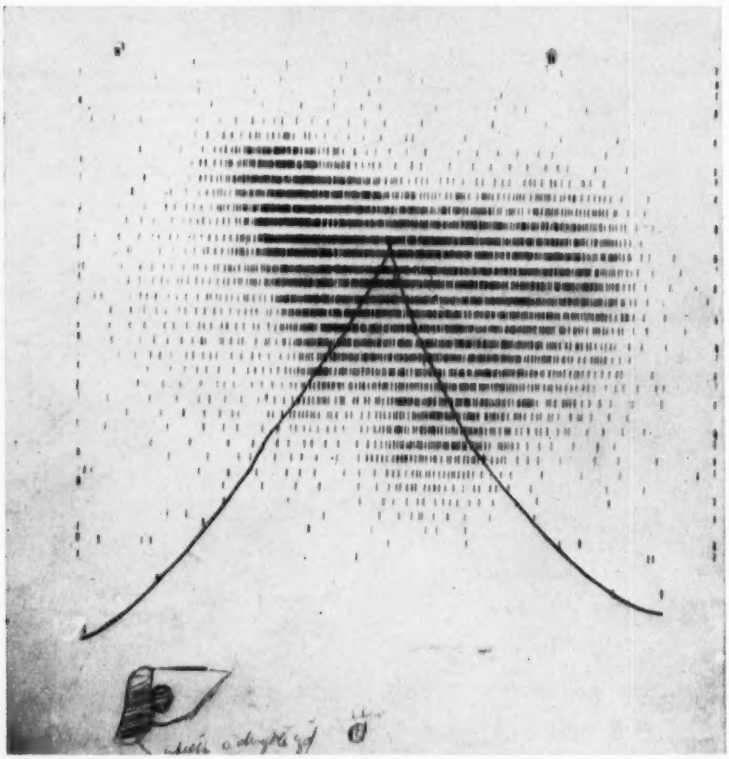

Fig. 6. Case study No. 6. Ruptured hydatid cyst and resulting subdiaphragmatic adscess.

No. 5. K. A. female, 25 years. The patient previously had three laparotomies and one thoraco-abdominal approach to multiple hydatid cysts in the liver. The scar of the abdominal operations was overlying a palpable mass in the liver, which was shown on the scintigram (Fig. 5) to be normal liver tissue displaced by a large mass farther to the right. A fourth operation through a subcostal incision revealed a cyst containing 3000 cc's of purulent hydatid fluid and daughter cysts.

No. 6. A. K. female, 20 years. The patient complained of pain in the right hypochondrium referred to the right shoulder. Casoni was positive. Liver scanning (Fig. 6) showed a large void area under the lower right ribs, displacing the liver to the left. Exploration through a subcostal approach revealed a huge extra-hepatic collection of pus (2000 cc's) connected to an intra-hepatic cyst containing 1000 cc's of pus and daughter cysts. Thus, a subdiaphragmatic abscess had been formed after localization of pus from a ruptured hepatic hydatid cyst.

CONCLUSION

From our first series of thirty cases, we found scanning to be helpful in the diagnosis of hyatid liver disease in the following circumstances:

1. In cases of hydatid cyst of the lung to exclude liver involvement, as in case No. 3.
2. Cases with palpable and enlarged liver, positive seriological tests, but no cystic mass on clinical examination, as in case No. 1.
3. Cases previously operated, with recurrence of original complaints. The seriological and other laboratory tests are not helpful, as they remain positive for many years following the removal of the cyst. Scanning helps in confirming the recurrence, localization, and planning the next approach, as in cases Nos. 4 and 5.
4. Localization of a large cyst displacing functioning liver tissue, as a guide to surgical approach. In distorted anatomy resulting from previous surgery, it is frequently difficult to distinguish by palpation between the cyst and displaced normal liver tissue, (as in case No. 6).
5. When there is a clinically suspicious mass with negative seriological reaction (as in case No. 2).

SUMMARY

The authors report their experience in the localization of hydatid cysts by liver scanning following the administration of collodial radiogold.

A high incidence of hydatidosis in Iraq results from unhygenic living conditions and the presence of sheep and stray dogs, fulfilling the requirements for the life cycle of *Echinococcus granulosus.*

On the scintigram the cysts are shown by voids, by irregularity of liver contour, or by gross displacement of functioning liver tissue.

The authors discuss the clinical usefulness of the procedure and present typical case studies with original scintigrams. They consider scanning to be of considerable value in countries where hydatidosis is endemic.

ACKNOWLEDGEMENTS

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Intracavitary Radioactive Colloidal Gold:[1] Results in 257 Cancer Patients

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INTRODUCTION

Since its description by Muller in 1949 (1), the intracavitary administration of radioactive colloidal gold Au-198 has come to be widely used in the management of disseminated cancer. A recent review of published cases (2) lists 2110 patients so treated; undoubtedly a great many more unpublished cases, however, have been treated with radiogold.

The radioactive gold is in the form of a colloidal suspension of a vast number of microscopic particles (10 trillion particles in 50 mc), each of which is a point source of radiation. Since the material is in metallic form, it is insoluble in body fluids, chemically inert and without the toxicity of gold salts. After introduction into a serous cavity, the particles tend to flocculate out into the linings of the cavity; there is a slight spread via the lymphatics but only an insignificant amount reaches the vascular circulation. There is negligible radioactivity in the excreta.

Radioactive gold has a half-life of 2.7 days, emmitting both beta particles and gamma rays. The beta particles have a maximum penetration in tissue of 3.8 mm; the half-path is only 0.4 mm. Since the therapeutic effect of the radioisotope in this situation is mainly due to the beta particles, it is apparent that the irradiation effects are essentially limited to the surfaces and first one or two mm of the serous linings and of any tumor tissue thereon.

During the eight-year period from April 1952 to March 1960, 257 patients received 332 instillations of radioactive colloidal gold at the M. D. Anderson Hospital and Tumor Institute.

METHODS

The radioactive gold is instilled into the cavity by a closed pressure system. The isotope is shielded by a lead pot until the moment of administration, so that

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[1]From the Endocrine-Isotope Service, Department of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas, and The University of Texas Postgraduate School of Medicine, Houston, Texas.

the radiation received by the therapy team is minimized. Instillation into the pleural cavity is via a thoracentesis needle; but instillation into the abdomen is by means of a polyethylene catheter threaded through the paracentesis trochar, the trochar then being removed and the wound sutured tightly closed about the tubing. Before instilling the radioactive material in patients without ascites, the peritoneal cavity is first insufflated with nitrous oxide gas to ensure that the needle or catheter is definitely in the peritoneal cavity and that no loculations are present. The gas is rapidly abosrbed (within one to two hours) and thus does not interfere with complete distribution and flocculation out of the isotope.

Automatic scintigrams of the region are performed to determine whether the gold has been accurately placed and well distributed throughout the cavity. After intraperitoneal administration, the patient is given an enema to doubly ascertain that the gold was not injected into the bowel. A set routine of turning the patient is followed, since we have observed that poor distribution results if the patient remains essentially in one position.

RESULTS

The number of patients and treatments with Au-198 are categorized in Table 1 according to the indications for treatment. This treatment has been administered in one of four situations:

1. to arrest recurrent malignant effusions;
2. to prevent the later development of effusions in patients with extensive abdominal carcinomatosis;
3. to treat patients with multiple diffuse peritoneal tumor seedings;

TABLE 1

INTRACAVITARY Au^{198} TREATMENT: NUMBER OF PATIENTS AND NUMBER OF TREATMENTS BY DISEASE CATEGORIES

Disease	*No. of Patients*	*No. of Treatments*
Recurrent malignant effusions	207*	281
Pericardial	1	1
Pleural	85	117
Peritoneal	126	163
Abdominal masses without ascites	9	9
Peritoneal seedings	15	15
Prophylaxis		
Spillage of ovarian cystadenocarcinoma	24	25
Perforation of carcinoma of uterine fundus	2	2
TOTAL	257	332

*Five patients received treatment to both the pleural and peritoneal cavities.

4. as prophylactic therapy following intraperitoneal tumor spillage.

In the first two groups, the radiogold is used for palliation only; in the latter two, it is given for possible cure.

Malignant Effusions

As palliation for recurrent carcinomatous effusions, 207 patients received a total of 281 treatment with radioactive gold. Response to treatment is graded as follows:

Excellent: No further fluid formation in a patient followed for six months or more.

Good: Marked slowing—one or two taps required over an extended period of six months or more; or no fluid formation in a patient surviving at least three months after treatment.

Fair: Appreciable slowing in rate of fluid formation; or cessation of fluid formation in a patient surviving only one to three months after treatment.

Poor or failure: Little or no change in rate of fluid formation.

Indeterminate: Patients dying within six to eight weeks of therapy; or results obscured by other therapy; or patient lost to follow-up.

As seen in Table 2, 65 per cent of the 85 patients treated for recurrent malignant pleural effusions and 57 per cent of the 126 patients treated for recurrent malignant ascites had beneficial palliation following radiogold administration. One patient treated for pericardial effusion showed no response. Although effusions caused by ovarian cancer and lymphoma appeared to show a better response than effusions caused by other tumors, this difference is not considered significant.

Survival time has ranged from one month to 83 months in ovarian cancer, averaging 11 months; from 1 week to 38 months in breast cancer, averaging 9.6 months; from two weeks to 26 months in lung cancer, averaging 5.5 months; from one week to 31 months in gastrointestinal cancer, averaging 8.1 months; from one week to 52 months in uterine cancer, averaging 7.4 months. One patient is still living with residual ovarian carcinoma at the time of her last follow-up examination, 83 months after therapy. It cannot readily be determined from this clinical data whether survival time is prolonged any by the Au-198 treatment. Studies with animal tumors, however, have demonstrated prolongation of survival time (3,4).

Carcinomatosis Without Fluid

Nine patients with massive abdominal and pelvic carcinomatosis but without fluid were treated (Table 3). The aim of treatment here was mainly to prevent distressing fluid formation and possibly shrink the masses or retard their growth temporarily. None developed ascites, whereas without treatment 30 per cent of these patients do so (5). Occasionally, there was temporary reduction in the size of masses or slowing of tumor growth. One patient with ovarian carcinoma is still alive 67 months after the treatment.

TABLE 2

RESULTS OF Au^{198} IN MALIGNANT EFFUSIONS

Pleural	*No.*	*E*	*G*	*F*	*P*	*I*	*% Worth While*
Primary							
Ovary	8	1	2	4		1	87
Breast	30		8	9	6	7	57
Lung	24	1	8	7	2	6	67
Uterus	5		1	2		2	60
Esophagus	2					2	0
Lymphoma	4	1	3				100
Misc.*	12	2	6		1	3	67
TOTAL	85	5	29	21	9	21	65

*Prostate 2; thyroid 2; kidney, testis, osteogenic sarcoma and unclassified sarcoma 1 each; 3 adenocarcinoma and 1 squamous cell carcinoma, primaries unknown.

Pericardial	*No.*	*E*	*G*	*F*	*P*	*I*	*% Worth While*
Ovary							0

Peritoneal	*No.*	*E*	*G*	*F*	*P*	*I*	*% Worth While*
Primary							
Ovary	66	14	15	13	6	18	64
Breast	6	2	1		1	2	50
Uterus	16	2	4	2	2	6	50
Stomach	8	1	1	2		4	50
Colon	7	3	1		1	2	57
Lymphoma	4	1		2		1	75
Pancreas	4	1				3	25
Misc.*	15	2	3	2	1	7	46
TOTAL	126	26	25	21	11	43	57

*Malignant melanoma, kidney, adrenal, testis, urethra, liver, mesothelioma 1 each; adenocarcinoma, primary unknown 3; undifferentiated metastatic tumor 1; mucocele of appendix with pseudomyxoma peritonei 2.

Peritoneal Seedings

Fifteen patients with diffuse peritoneal cancer seedings received radiogold instillation intraperitoneally. (Table 4). The primary tumor was ovarian in 13 cases and bowel in the other two. If the tumor implants are no larger than several millimeters in depth, intracavitary radioisotope therapy is theoretically a

highly suitable treatment. Six patients (all with ovarian primary) are living without evidence of disease up to 62 months following therapy (average 44 months). One patient later required surgery for resection of a solitary recurrent mass; it was found, however, that the seedings, identified histologically as carcinoma at the original operation, had disappeared. Two patients have died of unrelated disease (malignant hypertension, myocardial infarction) 72 months and 11 months after therapy; no evidence of residual tumor was found. Two patients are living with persistent tumor; five patients have died of their cancer.

Five patients in this group may not strictly fit the criteria for tumor "seedings:" two cases had apparent lymph node involvement (not resected) at the original surgery; one had a metastatic inguinal node removed three years before Au-198 therapy; and two required segmental intestinal resection for localized tumor invasion of the bowel. All five patients later presented with recurrent carcinoma and four have died of cancer.

TABLE 3

INTRACAVITARY RADIOGOLD TREATMENT IN PATIENTS WITH LARGE ABDOMINAL TUMOR MASSES BUT WITHOUT ASCITES

Patients	*No. Developing Ascites*	*Living*	*Dead*
9	0	1	8
Survival			
0–6 months			1
6–12 months			5
1–2 years			2
3–5 years			
5 years		1	

TABLE 4

RADIOGOLD TREATMENT FOR DIFFUSE PERITONEAL CANCER SEEDINGS

Patients	*Living*		*Dead*	
	Without Known Tumor	*With Tumor*	*Without Tumor*	*With Tumor*
15	6	2	2	5
Survival				
6–12 months			1	2
1–3 years	1	2		2
3–5 years	3			1
Over 5 years	2		1	

Prophylaxis

In this group are included 26 patients treated for intraperitoneal contamination with tumor cells, 24 of these cases following pre-operative or operative rup-

ture and spillage of ovarian cystadenocarcinoma and two cases of perforated carcinoma of the uterine fundus. Eighteen of the former group (75 per cent) were alive and well when last examined, twelve to 76 months after treatment, with an average follow-up period of 41 months. Two patients are alive with recurrent tumor and four patients have died of their cancer. Both patients treated for perforated uterine cancer were alive at their last follow-up visit without apparent residual cancer, five and a half and six years after the therapy.

The period of follow-up is too brief as yet to determine the over-all effectiveness of radiogold treatment in peritoneal seedings or following the rupture of malignant cysts. Complete five and ten-year follow-up data will be needed to provide this information. The present data, however, do indicate that cure cannot be anticipated in all of these patients.

COMPLICATIONS

Minor complications encountered following radiogold instillation intraperitoneally were transient nausea in 43 per cent, emesis in 30 per cent and diarrhea in 3 per cent of the patients. Of the patients treated intrapleurally, 32 per cent had some nausea, 13 percent had emesis but none developed diarrhea. Transient low-grade fever was seen in 30 per cent of patients treated intraperitoneally and in 10 per cent treated intrapleurally.

TABLE 5

INTRACAVITARY RADIOGOLD GIVEN AS PROPHYLAXIS FOLLOWING PERITONEAL CONTAMINATION WITH TUMOR CELLS

SPILLAGE OF OVARIAN CYSTADENOCARCINOMA

Patients	*Living*		*Dead*
	Without Known Tumor	*With Tumor*	
24	18	2	4
Survival			
1–2 years	3	1	3
2–3 years	4		1
3–4 years	3	1	
4–5 years	5		
Over 5 years	3		

CARCINOMA OF UTERINE FUNDUS WITH PERFORATION

Patients	*Living*
2	2
Survival	
Over 5 years	2

Malplacement of the radioisotope occurred in six instances: in 4 patients the material was inadvertently inserted into the colon but was promptly removed by repeated enemas and no serious sequelae ensued; in 1 patient, after instillation into the right chest, the radiogold was found well distributed throughout the peritoneal cavity indicating that the needle point must have moved to a position between the diaphragm and liver or else that there was an abnormal communication between pleura and peritoneal cavities, as described below; and in 1 patient the radioactive gold was injected mainly into the anterior abdominal wall. The use of polyethylene catheters and the nitrous oxide insufflation technique has, to date, successfully avoided further similar abdominal mishaps. In one other patient, considerable radioactivity was found in the left pleural space after intraperitoneal administartion. This case, plus similar experiences reported by others (6,7) suggest that communication is present in some patients (? due to tumor invasion) between these serous cavities. Five patients developed the so-called "frozen" or "plastic" abdomen. In each instance the patient had received a maximal dose of external irradiation prior to, or after, the radiogold treatment. In view of these unhappy experiences, this combination of Au-198 with heavy external irradiation was abandoned early in the series. Marked adhesion formation or fibrosis has not otherwise been a prominent feature.

DISCUSSION

The mechanism of action of radioactive gold in arresting recurrent malignant effusions remains obscure, as is indeed the mechanism causing the formation of these malignant effusions. The role of free tumor cells, weeping tumor surfaces, breakdown of the normal serosal barrier and plugging of the lymphatics of drainage by tumor cells has been previously discussed (8,10). In this series, free tumor cells, as assessed by cytological examination of the fluid, have variously disappeared, persisted or appeared after Au-198 treatment. Sanguinous effusions have usually become clear after therapy, although occasionally serous effusions have become sanguinous after the Au-198 treatment. The lactogenic dehydrogenase activity in the fluid has usually decreased markedly after therapy. Fibrous encasement over the surfaces of tumors, fibrinous and fibrous reaction on the serosal surfaces with subendothelial fibrosis and radiation endarteritis of subserosal blood vessels have been seen histologically in treated patients later coming to autopsy. On the basis of our early experience we concluded that the presence of large tumors precluded a good result in arresting the effusion, but more extensive experience has not substantiated this; these masses are no longer considered to be a contra-indication to Au-198 therapy; neither are the results obtained related to the type of tumor.

The dosage used in this series has been 100-200 mc in the pleural cavity and 150-200 mc intraperitoneally, with one or two doses given; giving more than two doses is not usually worthwhile.

Little information is yet available in the medical literature on the ultimate prognosis in patients treated for peritoneal seedings or contamination from ruptured cystadenocarcinoma; the number of patients reported is small and follow-up short or incomplete (10-15).

Radioactive colloids largely supplanted external irradiation therapy in the management of malignant effusions. Chemotherapeutic agents now have replaced the radiocolloids as initial treatment of choice in effusions caused by certain tumors, since these agents may not only arrest the effusion but cause tumor regression as well: in the lymphomas, Myeleran, Leukeran, 6-mercaptopurine, etc. are used; in ovarian carcinoma, Thio-Tepa, Cytoxan and phenylalanine mustard should be tried; in breast cancer, in addition to hormonal therapy and endocrine-ablative surgery, Thio-Tepa and Cytoxan are frequently effective; in carcinoma of the corpus uteri, progestational therapy may be indicated. In many other tumors, however, for which no effective chemotherapy is yet available (e.g. lung, gastrointestinal tract, pancreas, urinary tract), radioactive colloids appear to be the best agents for controlling the effusions. Nitrogen mustard given systemically or intracavitarily is used for its radiomimetic anti-tumor effects. In our experience the results using HN_2 have not appeared to be as good (46 per cent benefit) as with radiocolloids, and the incidence of complications (excessive fibrosis and adhesions) has been higher.

SUMMARY

During the eight-year period from April 1952 to March 1960, a total of 257 patients received 322 intracavitary instillations of radioactive gold at the M. D. Anderson Hospital and Tumor Institute. Included are: 207 patients referred for palliation of malignant effusions (126 peritoneal, 85 pleural and one pericardial application); nine patients treated to prevent development of ascites; 26 patients receiving Au-198 as prophylaxis after intraperitoneal spillage of the cancer; and 15 patients treated for multiple peritoneal implants. Sixty-five per cent of patients with pleural effusions and fifty-seven per cent of patients with ascites benefited from the radiogold therapy. Of the nine patients treated to prevent ascites, none developed fluid formation. Of special interest are the groups where Au-198 was given with curative intent: 20 of the 26 patients treated for carcinoma spillage are alive and well, with five of the patients now followed for more than five years; six of the 15 patients treated for diffuse peritoneal implants remain well, two others died of unrelated disease 2 and 6 years after Au-198 therapy, with no evidence of tumor found post-mortem.

Complications of therapy and their prevention are discussed, along with current concepts of the status of intracavitary radioisotopes in the management of disseminated carcinoma.

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ERRATUM

The following corrections are to be noted in the article entitled: "The Synthesis of Co-57 Tetraphenylporphinesulfonate and Its Use in the Scintillation Scanning of Neoplasms" by Doctors' Winkelman, McAfee, Wagner, and Long, which appeared in the May, 1962 issue of The Journal of Nuclear Medicine. 1) Page 249—fifth line of the second paragraph—the word elupted should read eluted. 2) Page 250—third line—the reference should read (3, 9) instead of (3). 3) Page 251—second paragraph under the heading of Discussion—a) fourth line, after word heat, insert reference (5). b) line six—reference should read (1). 4) seventh line—a) reference (2) should read (1). b) line seven—insert between hematoporphyrin and has—*and TPPS*. c) line nine—reference (6) should read (6, 7).

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PRELIMINARY PROGRESS NOTE[1]

Fluorine-18: A New Isotope for Bone Scanning[2,3]

**Monte Blau, Ph. D., Willibald Nagler, M. D.
and Merrill A. Bender, M. D.**

Buffalo, New York

The possibility of detecting bone lesions by isotope scanning before x-ray changes have become apparent is quite intriguing. Both Ca^{47} (1) and Sr^{85} (2) have been used for bone scanning and Corey, et.al. (3) have reported early detection of lesions not visible roentgenographically. Uptake of these agents has been found in areas of bone activity whether osteolytic or osteoblastic, suggesting that the mechanism of localization involves exchange with exposed bone crystal rather than a metabolic process. Presumably, therefore, any isotope capable of exchanging with bone crystal surface could be used for scanning. This report deals with one such agent, Fluorine-18, which has physical advantages over both Ca^{47} and Sr^{85}.

The difficulties of using Ca^{47} are associated with the high energy (1.31 MeV) of the principal gamma ray. The lead shielding and collimators available in most laboratories are inadequate for scanning at this high energy. Sr^{85} has the advantages of a lower gamma energy (.51 MeV) and no β emission. These are outweighed by the long physical half-life of 65 days. Since about 50 per cent of the dose is more or less permanently fixed in bone, the radiation, even from small scanning doses, is appreciable. A 50 microcurie dose has been estimated to deliver .33 rads total body and 2.3 rads to bone (2).

Fluoride ion has long been recognized as a "bone-seeker". In tracer amounts about 50 per cent of the dose is fixed in bone and 50 per cent is promptly excreted (4). Recent animal data indicate that fluoride accumulates in bone more rapidly and more selectively than calcium (5). In animal experiments in our laboratory we have found the F^{18} fluoride concentration in areas of regenerating bone more than ten times higher than in normal bone.

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[1]Preliminary Progress Note; see page 340.

[2]Supported in part by A. E. C. Contract # AT (30-1) 2455.

[3]From the Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo, New York.

Fluorine-18 emits a .65 MeV positron and has a half-life of 1.87 hours. The positron annihilation radiation provides .51 MeV photons suitable for scanning. The most important advantage of F^{18} is the short half-life. This permits large doses to be administered with very little radiation to the patient. Assuming 50 per cent of the dose fixed in bone and the other 50 per cent evenly distributed in the body the estimated dose per millicurie administered is .03 rads total body and .23 rads to the bone. It is therefore possible to give multimillicurie amounts of F^{18} permitting rapid scanning and making whole body bone surveys a feasible procedure. Scanning can be repeated as often as desired without interference from the previous dose.

The 1.87 hour half-life is also the most important disadvantage of this isotope. It requires that the scanner be in reasonably proximity to a reactor. Since the neutron flux of most university and medical reactors is high enough to produce adequate amounts of F^{18} by the irradiation of lithium carbonate (Li^6 (n, α) t, O^{16} (t,n) F^{18}) many hospitals find themselves within one or two half-lives of a suitable source of F^{18}.

Fig. 1.

Most of our clinical experience with this isotope has been limited to patients with known bone lesions. In each of 18 patients scanned the concentration of F^{18} in the lesion has been adequate for good visualization. Most of these patients have had metastatic bone disease (both osteolytic and osteoblastic) but areas of fibrous dysplasia and osteoporosis of disuse have also been visualized. The uptake in normal bone is very low compared to sites of active bone lysis or deposition. In two patients we have found uptake in sites of bone pain where no lesions could be found on x-rays. It is possible that these will prove to be early metastases.

Figure 1 shows the scan of an advanced osteolytic lesion and the corresponding x-ray. We administer 0.5 to 1 millicurie of carrier free F^{18} fluoride[1] in physiological saline 1-3 hours before scanning.

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[1]Supplied by Western New York Nuclear Research Center.

Date	*Names of Course or Meeting*	*Place*
***October*, 1962**		
2-5	**63rd Annual Meeting of the American Roentgen Ray Society**	**Washington D.C. U.S.A.**
9-11	**3rd Conference on Nuclear Reactor Chemistry**	**Gatlinburg, Tennessee**
29-31	**Colloquim on Fundamental Radiobiology**	**Rio de Janeiro, Brazil**
November, 1962		
19-23	**Symposium on Radioactive Dating**	**Greece**
25-29	**Winter Meeting of the American Nuclear Society and the Atomic Industrial Forum, including 10th Hot Laboratory and Equipment Conference and Atomic Fair**	**Washington, D.C. U.S.A.**
25-30	**Annual Meeting of the Radiological Society of North America**	**Chicago, Illinois U.S.A.**
December, 1962		
1-3	**Conference on the Modification of Radiation Injury by Bone Marrow Transplantation and Chemical Protection**	**New York, N.Y. U.S.A.**
June, 1963		
26-29	***10th Annual Meeting of the Society of Nuclear Medicine***	***Montreal, Canada***

Abstracts of Papers Presented at the Third Annual Meeting of the Society of Nuclear Medicine Southeastern Chapter, Atlanta, March 16-17, 1962

1. *The Effect of Hepatic Injury on the Metabolism of Sulfated Serum Proteins.* James L. Achord and John T. Galambos (Emory University Atlanta)

A total of 66 white male rats was placed on an 18% protein diet containing 0.06% 3-methyl-4-dimethylaminoazobenzene (DAB) and sacrificed at intervals of 2 to 24 weeks by exsanguination from 1 to 98 hours after 0.5 mc $S^{35}O_4$ was injected intraperitoneally. Three groups of animals were studied: normals, acute injury and chronic injury. The fraction of the injected dose was determined per milligram of perchloric acid insoluble (PAI) and perchloric acid soluble (PAS) serum proteins and in the electrophoretically separated serum albumin, α, β and γ globulins. Increased association of $S^{35}O_4$ was demonstrated in PAS in all animals on DAB and low-protein diet. The half life of PAS was prolonged in the group with acute injury, but the serum concentration was not altered. In the chronic group the decay rate was similar to that of normals, but the PAS concentration was increased. In normals the specific activity of α globulins was greater than that of the albumin, β or γ. In the chronic group the specific activity of all fractions was increased, but that of α globulins was decreased. Acute liver injury was associated with an increased association of S^{35} but a markedly decreased decay rate of PAS. The increase in the specific activity of PAS in the chronic group was not associated with a corresponding increase of that in the α globulin fraction.

Since Richmond (J. Biol. Chem. 234:2713, 1959) has shown that $S^{35}O_4$ association probably reflects glycoprotein synthesis, this study seems to indicate that there is an increase in the rate of synthesis of serum seromucoids (PAS) in DAB liver injury but that their rate of destruction is normal or prolonged. These findings are compatible with qualitative changes in this serum protein fraction.

2. *Recent Studies on the Carotid and Cerebral Circulation (A Work-In-Progress Paper).* H. C. Allen Jr. (Nuclear Medicine Laboratories of Texas, Texas Medical Center, Houston)

A diagnostic procedure as a screening test for the determination of impaired cerebral circulation is in the process of evaluation. The procedure uses a newly designed collimator, a $2'' \times 2''$ NaI crystal, and pulse height analysis. Some preliminary results in detecting early stenosis of the carotid arteries have been obtained.

3. *Interstitial Use of Radiating Microspheres.* Irving M. Ariel (Pack Medical Group, New York)

Available isotopes for interstitial use are either too large (gold radon seeds, or Au^{198} seeds) which makes distribution difficult and faulty, or they are too small (colloidal Au^{198}, or Cr $P^{32}O_4$) and traverse the lymphatics to distant sites. The availability of ceramic microspheres of relatively uniform size into which can be included various radioactive isotopes makes a satisfactory means of injecting isotopes intra-arterially into cancers especially in patients whose cancers are discovered to be inoperable at time of surgery.

In clinical trials we have used radioactive yttrium (Y^{90}) incorporated into microspheres 60 microns in diameter in a series of patients bearing inoperable cancer. The use of a special needle head increases the accuracy of the distribution of microspheres.

4. *The Distribution of Orally Administered Dicyclopentadienyliron^{59} in the Rat.* ARTHUR F. DRATZ (Radioisotope Service, Veterans Administration Hospital, Atlanta)

Since the synthesis of ferrocene, in which a covalently bound iron atom is "sandwiched" between two cyclopentadienyl rings, the organic chemists have described a very large number of similar compounds involving transitional and rare earth metals. We are currently engaged in a preliminary survey to determine the biologic response to some of these compounds. Ultimately, we hope that the peculiar properties of these compounds will lend themselves to specific applications in tracer technique.

Our initial study involves the gastric administration of dicyclopentadienyliron^{59} in oil solution to adult rats with subsequent determination of the distribution of Fe^{59} in the tissues and excreta at 1- to 6-day intervals. During this period about one-half of the administered activity is recovered in the urine, and about 6% in the feces. Initially, adipose tissue exhibits the highest concentration of Fe^{59}, but this decreases more than 10-fold by the sixth day. Liver activity increases for two days to a concentration higher than that observed in fat. For the next four days liver contains a relatively constant 20% of the administered activity. Other tissues have Fe^{59} concentrations much lower than that of the liver and these either remain relatively constant or decrease with time. Whole blood and plasma have the lowest concentrations of Fe^{59} initially. Thereafter, the concentration in plasma decreases and that of the whole blood increases.

5. *Demonstration of an Apparently Specific Hepatic Uptake Defect in Patients with "Gilbert's Disease."* JOHN T. GALAMBOS and JOHN R. MCLAREN (Emory University, Atlanta)

Radioactive iodide labeled iodipamide (cholografin) and rose bengal, when injected intravenously, allows evaluation of some parameters of liver function by external scanning. Results are quite similar and parallel conventional BSP retention studies. The advantage of the use of I^{131} iodipamide over BSP is that in the presence of edema or excessive obesity, body weight will not influence the dosage of iodipamide; only a single venipuncture is necessary; and if the injection infiltrates the delayed absorption can be corrected for. Its advantage over rose bengal is the much easier interpretation of the uptake plot and its use for predicting visualization of the biliary system on intravenous cholangiograms.

Seven I^{131}-labeled iodipamide studies were performed on 4 patients with nonhemolytic indirect hyperbilirubinemia ranging between 1.0 to 3.0 mg%. All 7 examinations showed a marked impairment of the hepatic uptake of iodipamide. The rose bengal uptake was normal in each of these patients when it was performed 2 hours after the I^{131} iodipamide test. The uptake defect was demonstrable in both patients in whom repeat studies were done whether the serum bilirubin was elevated or normal, and in one patient the BSP retention varied between 0 and 40%. These patients had no abnormality of serum protein, fluctuation or turbidity tests, alkaline phosphatase, or liver morphology. The gallbladder visualized normally. Schmid (Gastroenterology, 36:161) postulated a hepatic uptake defect on the basis of normal *in vivo* handling of α-glycones other than bilirubin. The marked depression of the hepatic uptake of a tracer dose of intravenously administered I^{131} iodipamide with normal uptake of I^{131} rose bengal demonstrates that an apparently specific hepatic uptake defect does exist and supports the view that some forms of recurrent, nonhemolytic, indirect hyperbilirubinemias may be due to a selective uptake defect of bilirubin.

6. *Large Particle Y^{90} Intravenously to Treat Lung Cancer.* EDGAR D. GRADY, WALTER SALE, and LUTHER C. ROLLINS (Atlanta)

Particles of Y^{90} just large enough to be trapped in capillary beds have been used to concentrate their beta radiation in lung cancers. In animals it was first shown that about 70% of these particles would remain in the lungs when a suspension in 12% dextran was given intravenously. Dogs tolerated up to six or eight millicuries per kilogram of total body weight.

Five patients with inoperable lung cancer (both primary and metastatic) have been treated by this method. Every patient has had both objective and subjective improvement. One is apparently free of disease three months after treatment. Three have had temporary regressions followed by advancing growth again. The fifth has disease that is still regressing.

Lesions were treated by intravenous injections when there was bilateral disease. If there was involvement of only one lung, the material was injected via a cardiac catheter into the pulmonary artery of the involved lung only. Two patients have been treated a second time too recently to be evaluated. There has been no side effect nor complication from the treatment.

7. *Clinical Applications of Iodine-125.* P. V. Harper, K. A. Lathrop, H. L. Endlich, W. Siemens, and R. W. Harrison (Argonne Cancer Research Hospital, Chicago)

While the potential advantages of I^{125} for certain clinical and experimental studies have long been recognized, its high cost and low purity when prepared by cyclotron bombardment of tellurium, have limited its use to animal material. Development of production methods using thermal neutron activation of xenon has made available large (half-curie) amounts of relatively pure (99%) isotope. Briefly, its advantages as compared to I^{131} are 1) The 60-day half-life provides long shelf-life and permits long-term metabolic studies. 2) The low energy dissipation rate greatly reduces radiation exposure of the patient in, for example, thyroid scanning. 3) The low energy of the principal photon radiation (27.3 kev) permits greatly reduced crystal size and shielding, and greatly enhanced detector and collimator efficiency. Even apart from these latter advantages, when the same microcurie dosage of I^{125} is used with unmodified equipment, it produces thyroid scans almost indistinguishable from those using I^{131} In I^{125} rose bengal liver scans, metastatic nodules on accessible surfaces of the liver appear with markedly enhanced contrast because the radiation originating in the underlying liver is attenuated in passing through the "cold nodule." Since I^{125} may be counted in an ordinary well crystal with 60 to 70% efficiency, studies involving small *in vitro* samples present no problem. There are, however, serious obstacles to the use of I^{125} where absorption in overlying tissue (HVL $\sim$ 2 cm is important, as in quantitative radioiodine uptake studies or brain scanning.

8. *Chromium (Cr^{51})-Labeled Hemoglobin Survival in Normal and Pyridoxine Deficient Rats.* Bergene Kawin and Jeng M. Hsu (Radioisotope Service and Biochemistry Research Laboratory, Veterans Administration Hospital and Johns Hopkins University, Baltimore)

Radioactive $Na_2Cr^{51}O_4$ was intravenously administered to normal and pyridoxine deficient rats of the McCollum strain. The hemoglobin and its associated Cr^{51} was measured in tail blood samples taken at intervals up to three weeks following injection. With the exception of a possible effect of the animals' weights on the amount of Cr^{51} bound to the hemoglobin, no differences were found between the average Cr^{51} specific activity of the hemoglobin of the two groups. The data demonstrated reduction of the apparent survival time as a first order function of the Cr^{51} label. It was possible to express these relationships as mathematical components of the apparent survival time, providing for evaluation of the true survival time as well as elution. By extension of these relationships to a given erythrocyte survival-time curve for humans, a method for graphical evaluation of erythrocyte decay and elution values is found. A variable rate of Cr^{51} elution was obtained.

9. *A Small Animal Linear Scanner: Calibration and Use.* Granvil C. Kyker, Takashi Honda, and John J. Rafter (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee)

The linear scanner designed for rapid screening of radioisotopic distribution in small animals uses a chart recorder (Varian Model G-11) to plot externally detectable radioactivity as a

function of longitudinal localization in the animal. The 2″ × 2″ NaI (T1) crystal detector is connected to a medical spectrometer. The adjustable slit between 4-inch lead collimators defines the range of isoresponse patterns. The table speed for the animal is mechanically variable to 20 inches per minute.

Calibration of the scanner included the isoresponse measurements for iodine-131 under various conditions. Three slit widths (⅛″, ¼″, and ½″) were studied in air, in large and small water phantoms, and in average rats with implanted I^{131} sources. The isoresponse directly above the slit was symmetrical laterally; also the isoresponse curve was essentially flat for lateral displacement of the sources beyond the cross-sectional dimension of a large rat. Collimation longitudinal to the scanner table is inverse to slit width.

The scanner has found application on rats injected by different routes with various radioisotopes including Na^{24}, K^{42}, Sc^{46}, Ca^{47}, Nb^{95}, I^{131}, and Ce^{144}. Repeated scans at increasing time intervals enable rapid interpretation of the metabolic distribution of a radioisotope as a function of time. Preliminary efforts toward quantitative interpretation were based on planimetric analysis of sections of the profile curve corresponding to arbitrary segments of the animal.

10. *Standardization of TSH Testing.* H. G. McDaniel and J. A. Pittman (Radioisotope Service, Veterans Administration Hospital and Department of Medicine, University of Alabama Medical Center, Birmingham)

Interpretation of the response of a patient to TSH (thyrotropin) stimulation has been impeded by lack of standardization of the procedures used in carrying out the test. We have determined the normal thyroidal, 4-,6-, and 24-hour I^{131} uptakes and PBI values and their variations in the population of this hospital, and applied 4 varieties of TSH tests to a similar population. These tests utilized either (a) a single injection of 5 USP units of commercial TSH, (b) a single injection of 10 units, (c) three daily injections of 5 units each, or (d) three daily injections of 10 units each.

Based on preliminary results in 31 euthyroid and 9 hypothyroid patients, the following conclusions can be drawn: The difference in TSH responsiveness between euthyroid patients and those with primary hypothyroidism is most marked when estimated by the 24-hour I^{131} uptake, the 4 and 6 hour uptakes giving less separation. The PBI response also gave separation approximately as good as the 24-hour thyroidal I^{131} uptake. Contrary to expectations, use of 10 unit single injections or multiple injections did not improve the stimulation attained with single injections of 5 units. Since there were 8 toxic reactions (nausea, vomiting, or thyroidal tenderness and swelling), in a series of 77 TSH tests done by another protocol, and since all except one of these occurred with doses greater than 5 USP units, the procedure used in Group (a) would seem the best for routine clinical practice. The normal response to this dose is an increase of 25% (of dose) over the control value, giving a final thyroidal 24-hour I^{131} uptake of 52.6%, and a final PBI of 6.8 μgm% (increment = 1.8 μgm %).

11. *Preliminary Experiences with Coronary Blood Flow in Dogs Using Iodine-125 (A Work-In-Progress Paper).* Faber McMullen, Hugh Hanson, and Herbert C. Allen, Jr. (Hermann Hospital, Houston)

The cardiac curves using I^{125}-labeled Hippurate and I^{131}-labeled Hippurate have been studied and compared in dogs. The curves were recorded with a 2-inch sodium iodide thallium activated scintillation crystal shielded only by a lead collar using pulse height discrimination. The curves were recorded in closed and open chested dogs, with lead shielding to define the portions of the curves contributed by heart, lungs, and chest wall. The cardiac events were timed by simultaneous recording of cardio-green dye dilution curves drawn from the right and left ventricle.

12. *Isointensity Patterns from Radioactive Colloidal Gold in Serous Cavities.* JACK M. MORGAN and RUSSELL WIGH (Medical College of Georgia, Augusta)

Patterns of the distribution of radiation around patients treated with Au^{198} were obtained. These patients had colloidal gold instilled either into a pleural cavity or into the peritoneal cavity for the treatment of effusions secondary to malignancies.

Diagrams indicating the dose in mr/hr around a patient in a conventional hospital room have been plotted.

13. *Collimation for* In Vivo *Counts of Cr^{51} and Fe^{59} in Spleen and Other Organs.* BILL M. NELSON and VICHAI POSHYACHINDA (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee)

The conditions required for an assay of I^{131} in the thyroid gland *in situ* have been stated, but for other organs and isotopes, external counting is only semiquantitative. Nevertheless, *in vivo* studies of the distribution of Cr^{51} and Fe^{59} have had rewarding clinical applications. We have tried to enhance the value of these studies by investigating the physical factors influencing external counts over such organs as the spleen, with primary attention to the effect of collimation. Isoresponse curves were plotted for a commercial collimator extending 86 mm from the front face of a $2'' \times 2''$ crystal, with a bore flaring to 80 mm distally. The collimated detector was applied to the side of a large plastic tank filled with water. A small Cr^{51} source was placed at multiple locations in the water and counts were recorded for each location. This was repeated with an Fe^{59} source, counting first the 1.1 and 1.29 mev gamma rays, and then the scatter at the 270 to 370 kev "Cr^{51} band." Similar curves were plotted for the same detector without the collimator so that the crystal could be applied directly to the water tank. Subsequently, spleen and liver phantoms containing Cr^{51} and Fe^{59} solutions were counted in the water tank. The data show that shorter collimators not only increase the sensitivity of external counting over an organ near the surface, but reduce the error due to faulty positioning and minimize "body background."

14. *Gastric Secretion of Tritiated Derivatives of Fluorene.* FRANCIS E. RAY (Cancer Research Laboratory, Department of Pharmaceutical Chemistry, University of Florida, Gainesville)

The secretion of tritiated 2-acetylaminofluorene and 2,7-diacetylaminofluorene by the stomach has been investigated. The latter alone causes adenocarcinoma of the stomach, and 41% more of the administered dose was found in the stomach wall; some 17% more of the former was found in the contents of the stomach. Over a period of time the increased percentage taken up might result in a large differential in the stomach tissue. On the other hand, the relative amount taken up may not be significant and the carcinogenicity may be attributed entirely to the greater potency of 2,7-diacetylaminofluorene. The basic nature of the compounds in any event enables them to reach the target area.

15. *The Radiotherapy of Malignant Diseases of the Chest.* BRYAN L. REDD, JR. (Robert Winship Memorial Clinic, Emory University, Atlanta)

With the high incidence of primary neoplasms arising within the thoracic cavity and the great frequency of metastatic implants into the chest, the radiologist is frequently called upon to treat various neoplastic processes involving the structures of the thoracic cavity.

The primary neoplasms that may arise in the thorax include carcinoma of the lung, and esophagus, malignant lymphomas arising within the mediastinum, malignant lesions arising in the thymus, neurogenic sarcomas or neuroblastomas arising in the mediastinum, mediastinal

teratomas, which may undergo malignant transformation, malignant mesotheliomas, primary bone sarcomas arising in the components of the rib cage, and rhabdomyosarcomas, which may arise from the striated muscle of the chest wall. Metastatic implants may occur in the lungs, mediastinal, or hilar lymph nodes or to the pleural spaces. These implants may arise from neoplasms occurring in any anatomical site and may be transported by blood stream, lymphatic channels, or by direct extension.

Case histories and radiographs illustrate several of the more frequent and unusual malignant lesions involving the chest.

16. *An Apparatus for* In Vivo $C^{14}O_2$ *Collection and Subsequent Scintillation Counting.* FRED SNYDER and PAUL GODFREY (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee)

We have developed a simple apparatus for collecting $C^{14}O_2$ (liberated *in vivo*) in a counting vial for liquid scintillation counting. The method involves no transfer of $C^{14}O_2$; the radioactivity can be counted immediately after the collection period. The exhaled gases (dried by passage through H_2SO_4) were circulated through the system by the kneading action of a sigma motor pump. The carbon dioxide was collected in a liquid scintillation vial containing 4 ml of hydroxide of Hyamine 10 X. Two such vials were connected to a Y tube with a pinch clamp used for diverting the gas flow into only one of the vials. A filter paper disc was inserted around the delivery tube going into the Hyamine to prevent spattering. The return system to the metabolism tube consisted of an empty vial (to serve as a trap for preventing the entry of H_2SO_4 into the counting system), a vial containing conc. H_2SO_4 (to absorb any metanol evaporated from the Hyamine), and a balloon containing about one liter of oxygen. After a collection period, the contents of the vial were mixed with scintillator (0.4% PPO and 0.01% POPOP in toluene) and the radioactivity measured with a Packard Tri-Carb liquid scintillation spectrometer. The appartus offers the advantage of permitting a large scale monitoring of the oxidation of carbon-14-labeled metabolites administered to small animals.

Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the September, 1962 issue must be in the hands of the Editor before August 1, 1962.

JOURNAL OF NUCLEAR MEDICINE 3:341-351, 1962

The Effect of Gamma Radiation on the Fibrinolytic System of Dog Lung and Its Modification by Certain Drugs: Relationship to Radiation Pneumonitis and Hyaline Membrane Formation in Lung[1,2]

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INTRODUCTION

The radiation reaction of human lung is characterized by edema, fibrosis, diminished leukocyte inflammatory response, hyalinization of arterial walls and alveolar hyaline membrane formation (1). In animals hyaline membrane formation is less striking than in humans. The primary reaction of animal lung tissue is characterized by interstitial edema, thickening of alveolar walls, increased cellularity, and the persistence of a fibrin-rich edema fluid. This latter concert of pathology has been termed "radiation pneumonitis" by Chu (2).

Recently our laboratory has reported an association in man and in dog between total-body gamma radiation, hyaline membrane of lung and diminished lung plasminogen activator (3). This paper presents our findings in dogs concerning the interrelationships between gamma irradiation of the lung, radiation pneumonitis and lung plasminogen activator. The modifications of lung response secondary to administration of cortisone, heparin, and actinomycin D are presented.

MATERIALS AND METHODS

The animals employed were male, mongrel, short-haired dogs which had been previously wormed and debarked by standard kennel techniques. The animals ranged from 10 to 15 kg of body weight. Standard diets were utilized. The animals were maintained in heated, semi-enclosed runs except during inclement

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[1]From the Radioisotope Laboratory and Radiation Exposure Evaluation Laboratory, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

The views expressed are those of the authors and do not necessarily reflect those of the Naval Service at large.

[2]Presented, in part, at the Eighth Annual Meeting of the Society of Nuclear Medicine, Pittsburgh, Pennsylvania.

[3]Present address: McCollum-Pratt Institute, Johns Hopkins University, Baltimore, Maryland.

weather when they were transferred to indoor stainless steel metabolism cages. This maneuver seemed to diminish the incidence of bacterial pneumonia.

Gamma radiation was administered by a Cobalt^{60} Theratron Jr.[1] containing approximately 1,000 curies of Co^{60}. The right hemithorax of each dog was irradiated in a field approximately 8 x 15 cm at a dose rate of 47 roentgens per minute. Total dose to the posterior aspect of the right thorax varied between 1,500 to 2,000 rad. The radiation dose was administered in one continuous exposure to dogs sedated with 40 mg/kg of intravenous nembutal sodium.

Assay of lung plasminogen activator was by means of bovine fibrin plates prepared and utilized according to the technique of Fleming and Norman (4). Citrated bovine fibrinogen was obtained from Armour Laboratories,[2] and thrombin USP,[3] from Parke, Davis and Company. One-half of the prepared plates were heated to 90°C for 20 minutes to destroy absorbed plasminogen. Cubes (5 x 5 mm) of both lungs were incubated at 37°C for 18 hours. Lysis is defined as a clear liquid zone surrounding the tissue cube. Lysis of the unheated fibrin, but not the heated fibrin, is interpreted as indicating the presence of lung plasminogen activator whereas, lysis of both heated and unheated fibrin indicates the

[1]Atomic Energy of Canada Ltd., Ottawa, Canada.
[2]Armour Labs., Kankakee, Illinois.
[3]Parke Davis and Co., Detroit, Michigan.

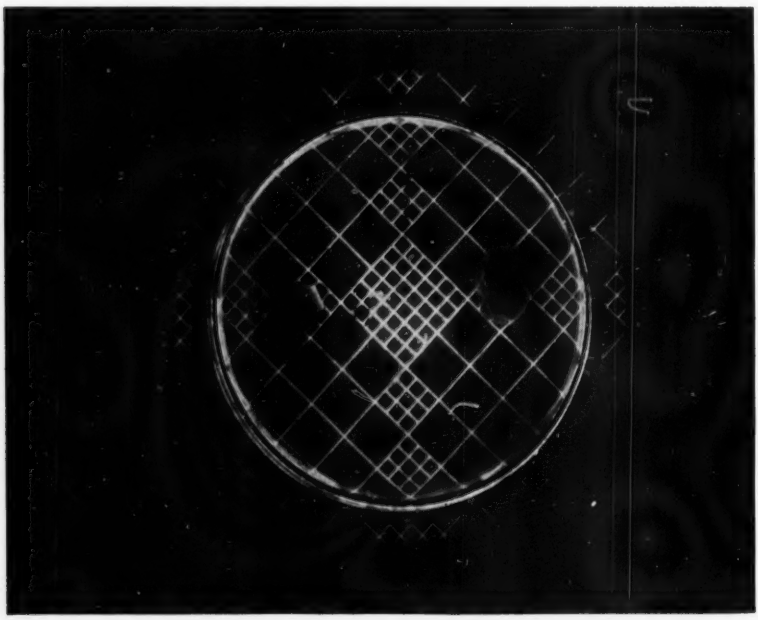

Fig. 1. Photograph of typical unheated fibrin plate assay. The dog lung tissue on the left is the nonirradiated control. Note the clear lysis zone about this lung tissue as contrasted to the lung tissue on the right from the irradiated chest.

TABLE 1

SINGLE EXPOSURE COBALT^{60}

GAMMA RADIATION TO RIGHT HEMITHORAX

Dog No.	*Radiation Dose (rad)*	*Examined Post-Radiation (weeks)*	*Bacterial Pneumonia*	*Radiation Pneumonitis*	*Hyaline Membrane*	*Lung Activator*	*Activator Inhibitor*
492	1500	11	−	+	+	−	+
486	1500	15	−	+	+	−	+
442	2000	3	−	+	−	−	+
327	1500	6	−	+	−	−	−
110	1500	11	+	+	−	−	−
330	1500	12	+	−	−	proteolytic	proteolytic
282	1500	12	+	−	−	proteolytic	proteolytic
231	1500	14	+	−	−	proteolytic	proteolytic

− indicates negative
+ indicates positive

TABLE 2

EFFECT OF HEPARIN

Dog No.	*Radiation Dose (rad)*	*Examined Post-Radiation (weeks)*	*Bacterial Pneumonia*	*Radiation Pneumonitis*	*Hyaline Membrane*	*Lung Activator*	*Activator Inhibitor*
420	2000	6	−	+ (no fibrin)	−	−	+
418	2000	10	−	+ (no fibrin)	−	−	−
421	2000	10	+	−	−	proteolytic	proteolytic

− indicates negative
+ indicates positive

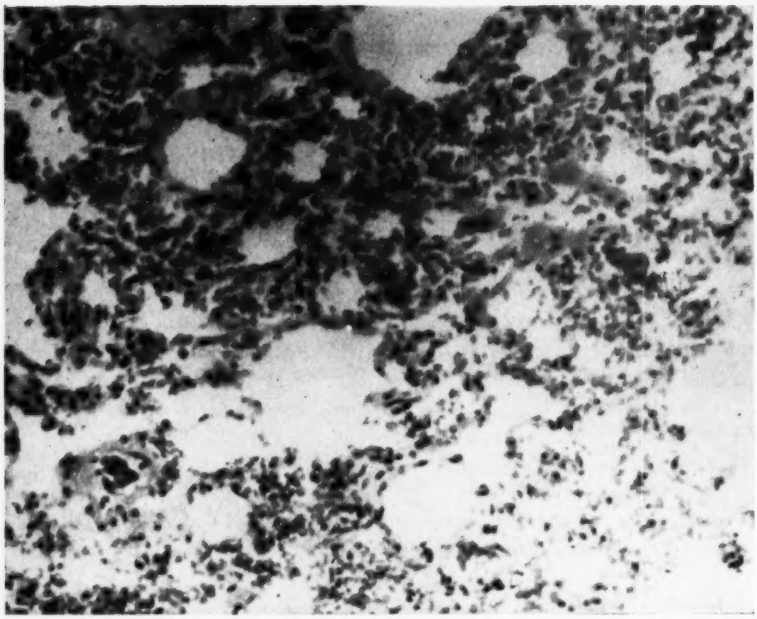

Fig. 2. Section of dog lung showing radiation pneumonitis. Note the interstitial edema, thickened alveolar walls, increased cellularity and areas of persistent fibrin-rich edema fluid. Hematoxylin and eosin, X 350.

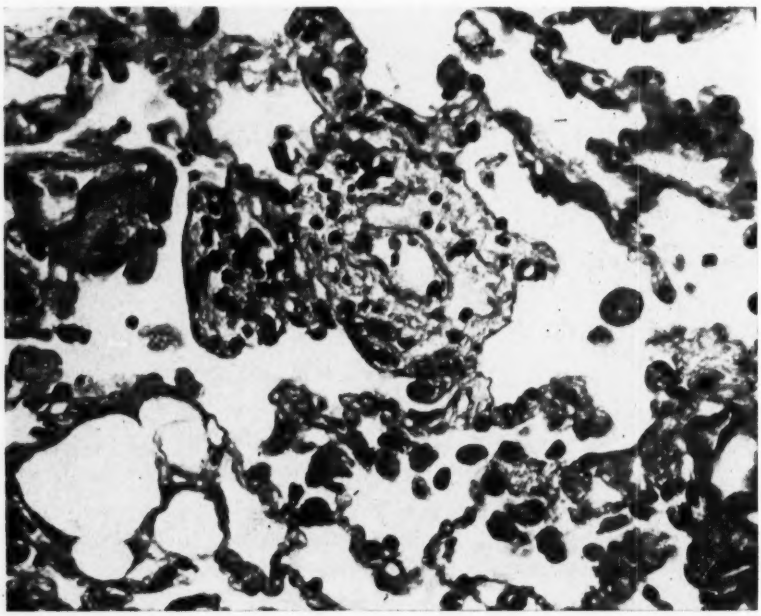

Fig. 3. Section of dog lung showing radiation hyaline membrane. Membrane formation is particularly prominent in the lower right portion of the photograph. Note the large rounded "dust cell" of Macklin, which has staining properties like alveolar epithelium. Hematoxylin and eosin, X 750.

presence of nonspecific proteolysis (Fig. 1). This technique is considered sensitive, specific, and simple (5).

Inhibitor was assayed according to Lieberman (6). Ten per cent lung homogenates were prepared in physiologic saline from the irradiated right and control left lungs of the dog. These homogenates and 50 per cent mixtures of each were incubated on the aforestated fibrin plates. Inhibitor is present when the right irradiated lung homogenate prevents lysis by the left control lung homogenate on unheated fibrin.

Five hundred thousand units of procaine penicillin G and 0.5 grams of streptomycin sulfate were given deep, subcutaneously, thrice weekly to the radiated animals as a prophylaxis against pneumonia. Cortisone acetate, 50 mg, was administered orally at 8 hour intervals to five animals (Table 2).

Heparin sodium injection, USP 20,000 units per ml, was employed in 3 dogs at a dose rate of 5,000 units every 12 hours until the animal was sacrificed (Table 3).

Actinomycin D[1] in dosages of 15 μg/kg were utilized intravenously in 4 dogs. The first actinomycin D dose was given just prior to lung irradiation and repeated for four consecutive days thereafter (Table 4).

RESULTS

The right hemithorax of seven dogs was treated with 1,500 rad and one ad-

[1]Kindly supplied by Clement A. Stone, Ph.D., Director, Merck Institute for Therapeutic Research, West Point, Pennsylvania.

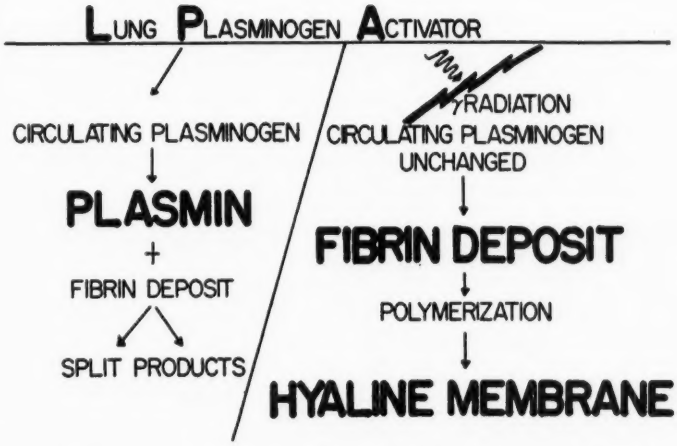

Fig. 4. Diagram illustrating the function of lung plasminogen activator. The scheme to the left of the center dividing line illustrates the normal sequence of events. Gamma radiation has "blocked" the activation of plasminogen on the right of the diagram and this leads to the formation of hyaline membrane.

ditional animal received 2,000 rad to the right chest (Table 1). These animals received only penicillin and streptomycin in addition to the radiation. Five of these animals had radiation pneumonitis as defined by Jennings and Arden (7). This consisted of interstitial edema, thickening of the alveolar walls, increased cellularity, and a persistent fibrin-rich edema fluid (Fig. 2). Two of the five animals developed extensive hyaline membranes of lung (Fig. 3). None of the five animals had detectable lung plasminogen activator. Lung homogenates from three of the seven animals were positive for lung plasminogen activator inhibitor. Animal #110 had a microscopic bacterial pneumonia. Three animals had extensive right lung pneumonia which yielded nonspecific proteolytic reactions by fibrin plate assay. The lung histology of these three animals was that of pneumonia which obscured the radiation characteristics.

Three dogs were given heparin sodium, 5,000 USP units, twice daily, into their depot fat, 3 days prior to irradiation of the right chest and continuing until the animals were sacrificed (Table 2). These animals received 2,000 rad to the right lung, and at autopsy the right lungs from two of the animals had radiation pneumonitis associated with nondetectable lung plasminogen activator. Right lung homogenates from dog #240 revealed lung activator inhibitor. Dog #421 had severe bilateral bacterial pneumonia and the fibrin plates showed nonspecific proteolysis. A striking decrease in fibrin deposition was noted in the right lungs of dogs #418 and #420.

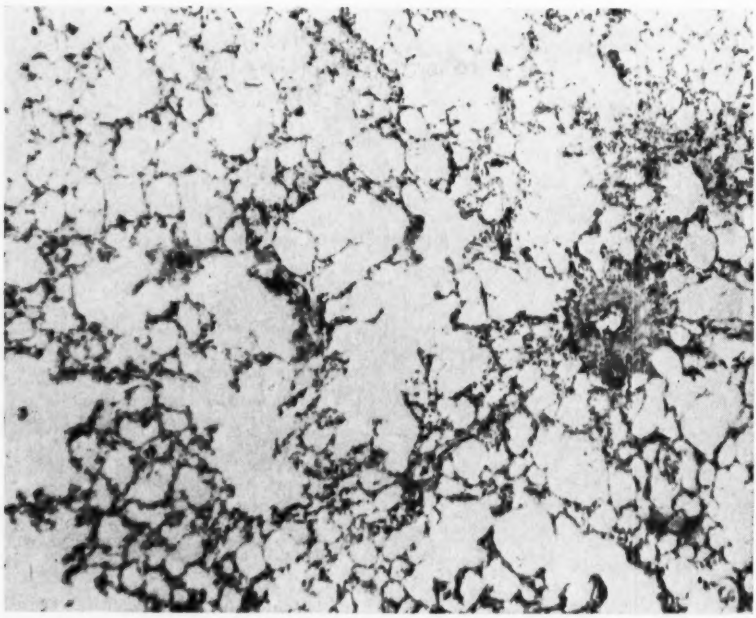

Fig. 5. Section of irradiated dog lung which had been protected by the administration of actinomycin D. Note the normal delicate noncongested alveolar septa. Hematoxylin and eosin X 100.

Five dogs were given 10 mg/kg cortisone acetate, orally, three days prior to irradiation and daily thereafter until sacrificed (Table 3). At autopsy, three of these animals had radiation pneumonitis associated with negative fibrin plate assays for lung plasminogen activator. Homogenates from two of the irradiated lungs showed the presence of a lung plasminogen activator inhibitor, whereas, #192 was negative for inhibitor. Dog #443 had bacterial pneumonia and fibrin plate assay revealed nonspecific proteolysis. The questionable assay of dog #350 was characterized by a transparent zone about the radiated lung tissue on the unheated fibrin which was not completely fluid.

Four dogs were given 15 μg/kg actinomycin D intravenously, immediately prior to irradiating their right lungs with 2,000 rad. The actinomycin D dose was repeated on four subsequent, consecutive days post-irradiation. Results are summarized in Table D. Animal #460 died suddenly at one week, secondary to a pulmonary artery embolus. Both lungs from this animal appeared normal histologically and yielded positive lung activator assays. Three other animals were sacrificed at 9 and 11 weeks. All of their lungs were normal histologically, and all had intact lung plasminogen activator systems.

DISCUSSION

Pathologic similes between radiation hyaline membrane of lung and neonatal

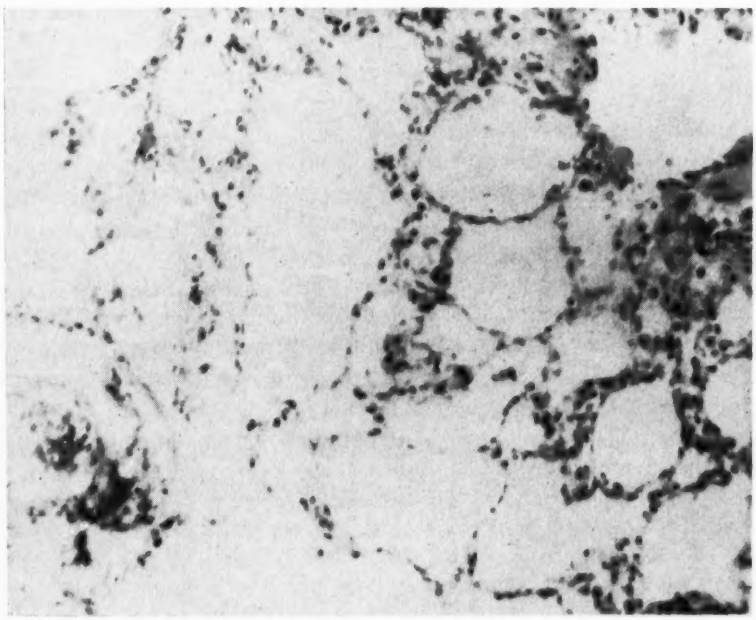

Fig. 6. Close up view of the dog lung tissue illustrated in Figure 5. Note the retention of of normal alveolar histology. The gray appearing areas on the lower left are smooth muscle fibers. Hematoxylin and eosin X 750.

TABLE 3

EFFECT OF CORTISONE

Dog No.	*Radiation Dose (rad)*	*Examined Post-Radiation (weeks)*	*Bacterial Pneumonia*	*Radiation Pneumonitis*	*Hyaline Membrane*	*Lung Activator*	*Activator Inhibitor*
350	1500	2	+	−	−	?	−
311	1500	4	−	+	−	−	+
327	1500	12	−	+	−	−	+
443	1500	12	+	−	−	proteolytic	proteolytic
192	1500	14	−	+	−	−	−

− indicates negative
+ indicates positive
? questionable assay

TABLE 4

EFFECT OF ACTINOMYCIN D

Dog No.	*Radiation Dose (rads)*	*Examined Post-Radiation (weeks)*	*Bacterial Pneumonia*	*Radiation Pneumonitis*	*Hyaline Membrane*	*Lung Activator*	*Activator Inhibitor*
460	2000	1	−	−	−	+	−
493	2000	9	−	−	−	+	−
494	2000	9	−	−	−	+	−
461	2000	11	−	−	−	+	−

− indicates negative
+ indicates positive

hyaline membrane disease have been noted previously (8). Gitlin and Craig (9) have pointed out by immunologic technique, that neonatal hyaline membrane originates from a fibrin matrix which becomes highly polymerized. Their findings were confirmed morphologically with the electron microscope by Van Breemen et al. (10). The latter authors also concurred with Gilmer and Hand's (11) finding of an early focal fibrin accumulation about the lung capillaries in neonatallhyaline membrane disease.

Recently, Lieberman (12) has called attention to defects in lung fibrinolytic activity in children with neonatal hyaline membrane disease. This author reasons that since lung plasminogen activator is a relatively insoluble enzyme, its action is primarily local. When fibrinous material is deposited in or about an alveolus, it is the function of lung plasminogen activator to convert circulating plasminogen to plasmin which then can effect fibrinolysis (Fig. 3). Defects in this system may lead to fibrin deposition and hyaline membrane formation. Ultimately, fibrosis follows prolonged fibrin deposition (13).

Our data indicate that 1,500 to 2,000 rad gamma radiation to a dog's hemithorax are sufficient to produce radiation pneumonitis and hyaline membrane of lung. It appears that hyaline membrane formation represents a further polymerization of the fibrin-rich edema fluid of radiation pneumonitis, as membrane formation was not seen prior to the eleventh post-radiation week. A defect in lung plasminogen activation was always present in radiation pneumonitis and hyaline membrane of lung. This defective lung activation of plasminogen was irregularly associated with an inhibitor. Our concept of the pathogenesis of radiation pneumonitis and hyaline membrane is summarized in Figure 3.

As has been noted by Berdjis (14), irradiation of the lung increases its susceptibility to infection. Presumably, bacterial proliferation elaborates sufficient proteolytic enzymes to destroy the fibrin-rich edema and hyaline deposits; yielding nonspecific proteolytic results by fibrin plate assay.

Anticoagulants have been employed in animals (15) and man (16) to modify, or prevent, radiation pneumonitis and hyaline membrane formation. The injection of heparin sodium, 5,000 USP units, into the depot fat of three, 10 kg dogs altered the deposition of fibrin in two of the animals, but did not protect lung plasminogen activator (Table 2). Histologically, one could still discern radiation pneumonitis.

Rubin et al. (17) have reported the efficacy of adrenocorticords in suppressing human radiation pneumonitis. Berdjis (14) studied the effect of cortisone on the irradiated rat lung and originally concluded that it had a beneficial effect. Subequent studies (18) by that author, led him to conclude that cortisone potentiated irradiation effects on rat lung and, in particular, the irradiation effects on rat kidney. Attempts to modify the response of dog lung to Co^{60} gamma radiation were unsuccessful at an oral dose level of 50 mg of cortisone acetate every eight hours. These data are summarized in Table 3.

D'Angio *et al.* (19), Chan *et al.* (20) and many others (21) have reported potentiation of the effects of irradiation by means of actinomycin D. Fifteen

micrograms per kilogram of body weight of actinomycin D were administered intravenously to four dogs just prior to irradiating the right lung with 2,000 rad Co^{60} gamma radiation (Table 3). This dose of actinomycin D was repeated for four consecutive post-radiation days. At autopsy, 9 to 11 weeks post-irradiation, the irradiated lung was morphologically normal (Fig. 5). Fibrin plate assays revealed normal lung plasminogen activator in all four dogs. This protective action of actinomycin D was fully unexpected, and perhaps, is related to cytostatic properties of the drug. Further studies are in progress to elucidate the mechanisms involved in this "protective" effect of actinomycin D.

SUMMARY

The pathogenesis of radiation pneumonitis is associated with defective lung plasminogen activation. This defect appears by the end of the first post-radiation week in dog lungs which have been exposed to 1,500 to 2,000 rad Co^{60} gamma radiation. With the lung's fibrinolytic system thus paralyzed, fibrin deposits persist leading to hyaline membrane formation, and ultimately, fibrosis of the lung.

Cortisone and heparin in the doses employed, failed to protect or potentiate, the effects of Co^{60} gamma radiation on the histology and activator enzymes of dog lungs. Heparin did seem to diminish fibrin deposition, however, sufficient histologic defects persisted to allow one to diagnose radiation pneumonitis.

Actinomycin D, 15 μg/kg, administered intravenously just prior to, and for four subsequent post-radiation days, fully protected the lungs of four, 10 kg dogs given 2,000 rad to the right hemithorax. Histologically, these lungs were completely normal and lung plasminogen activator was readily detectable in all. The mechanism of this protective action of actinomycin D is not presently understood.

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Preliminary Evaluation of the Iodine-132 Solution From the Brookhaven Te-132—I-132 Generator[1]

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INTRODUCTION

Despite its short half-life (2.33 hours), iodine^{132} (I^{132}) is now available in a chemical form and in quantities suitable for clinical applications at locations remote from a nuclear reactor or cyclotron. This has been accomplished by the development of a small, simple generator (the "cow") containing the relatively longer-lived parent isotope (tellurium^{132}, 77 hours) from which the daughter I-132 may be "milked" as needed. The limitations imposed by the transit time from a primary source of radiosotopes are shifted from those set by a 2.33 hour half-life to those set by a 77-hour one. It is, therefore, feasible to deliver useful quantities of I-132 anywhere in the world.

The present study was designed to evaluate the Brookhaven National Laboratory (BNL) Generator for I-132 in a nuclear medicine laboratory of a general hospital under such circumstances. Studies in this report are concerned with the handling and safety of such an isotope, but do not include its use in patients. Significant data pertaining to I-132 from other authors has been included for completeness.

PRINCIPLE OF PRODUCTION OF I^{132}

Tellurium-132 (Te^{132}) is available as a uranium fission product. It decays to I-132 by beta emission. The I-132 in turn decays to stable xenon^{132} (Xe^{132}) by beta and gamma emission. It has been determined that after all of the I-132 has been separated or "milked" from the Te-132 and fresh I-132 allowed to form, the I-132 will reach maximum activity in 12.1 hours and be in secular equilibrium with the parent Te-132 after 16 hours. Thereafter, the I-132 will be decaying with

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an "effective" half-life equal to the parent Te-132 (77 hours). However, once a sample is separated from the parent, the daughter I-132 decays with its own half-life of 2.33 hours. Thus the parent Te-132 provides a continuing source of I-132 from which quantities of I-132 can be obtained at will (1).

The I-132 generator[1] consists of a small (approximately 3 × 15 cm) plastic sleeve charged with pile produced Te-132 adsorbed on alumina. The I-132 solution is obtained by allowing 15 ml of weak ammonia solution (0.01 M − NH_4OH) to seep through the generator and collecting the effluent ("milking").

DECAY SCHEME OF I-132

The decay scheme of I-132 is presented in Figure 1. It is seen that there is a complex beta and gamma spectrum with maximum values of 2.13 MEV and of 2.2 MEV, respectively (2). The I-132 passes through this complicated cascade to decay to stable Xe-132. The latter substance is inert and presents no physiological problems.

[1]Available from Brookhaven National Laboratory, Upton, N. Y.

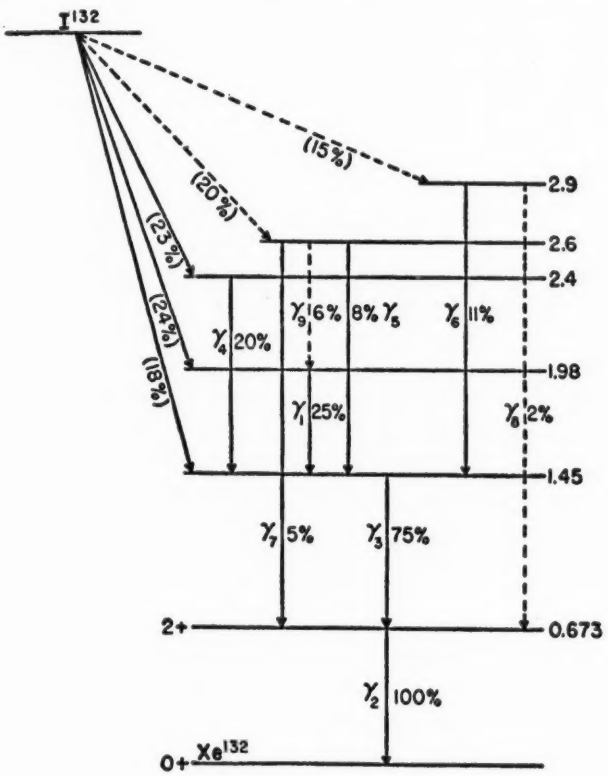

Fig. 1. Decay Scheme of I-132.

ASSAY OF I-132

The effluent is diluted in a suitable manner with water, usually between 1/5000 and 1/100, and counted in duplicate in a scintillation well counter. Assay is accomplished by comparative counts using a cesium[134] standard[1] (0.03 μc). This standard has an energy spectrum closely resembling I-132, and produced a satisfactory decay curve over the period examined in the report (9 months). The equation used for calculating I-132 specific activity follows:

(1) Specific Activity (μc/cc) of undiluted I-132 at "milking" time T_0

$$\frac{\text{Counts/minute @ } T_0 \times \text{Dilution factor}}{\text{Counts/minute for/ Cs-134 standard/}\quad \frac{\text{activity } (\mu\text{c})}{\text{Cs-134 standard}}}$$

or

(2) $$\frac{\text{c/m } T_0 \times \text{Dilution factor}}{\text{c/m/}\mu\text{c Cs-134}}$$

The total I-132 yield may be obtained by multiplying the specific activity by the effluent volume.

MEASURED GENERATOR YIELD

Assay of the generator effluent at our laboratory (SJH) after time for attainment of secular equilibrium had elapsed was compared with the BNL assay to obtain an efficiency factor which estimated the I-132 yield in terms of Te-132 charge calculated to the same time. Summary values (as averages) for 9 generators follow: BNL assay (as Te-132) 12.7 mc; SJH assay (as I-132) 0.53 mc/cc; total activity (as I-132) 7.9 mc; efficiency 62 percent.

COMPOSITION OF SOLUTION TO BE GIVEN

An aspect of the use of I-132 to which consideration has been given is the composition of the solution which the patient ingests. Analysis of this solution at the BNL Hot Lab (1) has been reported (Table 1).

TABLE 1

Analysis of the I-132 Solution (1)

Volume	15 ml (approximately)
Salts	0.01 M Ammonia
I (Stable)	None
Te (Stable)	None (carrier-free)
I-131	Less than 0.3%
Te-132	Less than 0.001%
I-132	Microcuries to decicuries as desired.

All values are "per milking" of the generator. The only component of toxicological interest besides I-132 is stable tellurium.

[1]Available from BNL.

TELLURIUM CONTENT OF EFFLUENT

The absence of tellurium in the solutions from the present model generator makes any discussion of tellurium content of the effluent solution of academic interest only. Previous model generators sometimes allowed biologically significant amounts of tellurium to appear in the effluent resulting in a garlic odor (dimethyl telluride) on the breath after ingestion. At higher levels of tellurium ingestion frank toxic symptoms have been reported, but none have been noted with BNL generators.

To eliminate any possibility of tellurium toxicity it was considered desireable to assay the effluent solution to determine if tellurium was a significant contaminant. Chemical assay was performed by a modification of the method described in Feigl (3). One drop of the effluent was put into each of two depressions of a three-depression white porcelain slide. One drop each of concentrated hydrochloric acid and 50 percent hypophosphorus acid (H_3PO_2) was then put into each of the three depressions. This provided a duplicate test of the effluent solution and a control of the reagents. The reactants were evaporated to near dryness by slow heating under an infra-red lamp. Fumes from the reaction which are radioactive were aspirated by using a large glass funnel inverted over the reactant slide. The funnel stem was connected in series of two U-tubes filled with activated charcoal,[1] and a bottle containing 33 percent KOH solution. Mild suction from a faucet vacuum pump provided a stream of air through the air scrubbers. Radioactive recordings at the last purifier (KOH solution) showed activity values less than 50 percent above background.

The effluent of 9 generators showed no evidence of any precipitate in 50 tests in duplicate. This implies that if any tellurium is present then it is present in less than detectable amounts (i.e. less than 1×10^{-6} gm), since standard solutions of sodium tellurite tested in a similar manner showed an easily discernible precipitate at this level. This value is well below any biologically significant toxicity reported in the literature (4-11).

RADIOACTIVE CONTAMINATION

Radioactive contamination of the I-132 effluent by other isotopes was estimated by determining the counting rate of the same sample in duplicate for various periods of time after "milking." Comparison of the counting rate at day of "milking" with the rate one day later (Day 1) showed a contamination of 1% or less. A time plot of the count rate for the period from Day 1 to Day 8 showed a progressively decreasing activity. Crude estimates of the curve suggested two components, one of about three days half-life, another of eight days. No further effort was made to identify these materials, but they were presumed to be Te-132 and I-131. The data were interpreted to suggest that radioactive contamination of the I-132 solution was negligible. The data do not rule out the possible presence of one or more isotopes with half-lives as short as that of I-132. The method of preparation of the generator and the BNL analysis do not suggest that any other isotope species are to be expected, however.

[1]ACC-6/14X National Carbon Co., Cleveland, Ohio.

BIOLOGICAL DISTRIBUTION

Since I-132 is one of the several isotopes of iodine, and since the biological distribution of other isotopes of iodine (I-130, I-131) is well known, the problem of distribution of I-132 will be covered only briefly. Relative radiation doses (12) for I-131 to various organs of the body have been reported as blood 1, kidney 8, stomach 8, mouth 20, thyroid 100.

These values suggest that in human beings nearly all of the I-131 localized in the thyroid with much lesser amounts in the mouth (salivary glands) stomach, kidney and blood. Other tissues have essentially negligible amounts in terms of immediate radiation effects. Gonads may be altered in their genetic function by relatively small radiation dosages, however, which puts them in a separate category.

I-132 shows a decreased radiation dosage to the thyroid by a factor of 1/24 when compared with I-131. (Table 2) For a nominal 15 μc I-131 tracer (14) an

TABLE 2

A COMPARISON OF I-131 AND I-132 (modified from Ref 13)

Isotope	*Maximum beta-energies MEV*	*Gamma-energies MEV*	*Half-life*	*I γ Dose Rate* rad/mc hr @ 1 cm*	*Thyroid Radiation** (rad)*	*General Body Radiation (rad)*
	(a, b)					
I-131	0.250 (2.8%)	0.080 (2.2%)		2.23	150	0.4
	0.335 (9.3%)	0.163 (0.7%)	8.04			
	0.608 (87.2%)	0.284(5.3%)	to			
	0.815 (0.7%)	0.364 (80%)	8.16			
		0.637 (9%)	days			
		0.722 (3%)				
	(a, b)					
I-132	0.73 (15%)	0.510 (25%) (c)		9.6	6.7	0.02
	0.97 (20%)	0.620 (6%)	2.33			
	1.16 (23%)	0.665 (100%)	± 0.02			
	1.60 (24%)	0.768 (75%)	hours			
	2.13 (18%)	0.960 (20%)				
		1.16 (8%)				
		1.40 (11%)				
		1.96 (5%)				
		2.2 (2%)				

* Per hour, 1 cm from an unfiltered source of 1 millicurie (Ref 14).

** From 100 microcuries given to a 70 Kg human with 30 per cent uptake in a 20 gm thyroid.

(a) The percentage of disintegrations in which there are emissions of this intensity.

(b) Hollander, Perlman, and Seaborg, "Table of Isotopes," UCRL-1928, December 1952.

(c) Finston and Bernstein (Brookhaven) (Ref 2).

N. B. Dosage calculations for thyroid and general body radiation were independently checked.

equal I-132 thyroid dose would be given by approximately 450 μc I-132. The shorter half-life of I-132 and the greater decay of the isotope in extra-thyroid tissues indicates that relatively more of the radiation will be delivered as whole body dose for I-132 than for I-131.

For a nominal intravenous 15 μc dose of I-132 in a 70 kgm human with no thyroid uptake, and negligible excretion the whole body radiation dose is calculated as 2.3 millirad (appendix). Similarly where the uptake is entirely thyroid the thyroid dose would be expected to be 1.8 rad (Table 3). These are maximum theoretical limits of radiation dose expected, simulating extreme hypothyroidism (zero uptake) and hyperthyroidism (100% uptake). These are tolerable values for medical testing purposes (15-18).

The gonadal radiation, while within the "safe" limits, may have genetic effects which cannot be evaluated. The radiation dose to the testes from I-131 has been reported (19) as ranging from 0.001 percent to 0.011 percent of administered dose for 4 patients. The ovaries of 3 patients showed 0 to 0.006 percent of the dose. These values referred to a nominal 15 μc I-131 tracer yield an approximate radiation dose range from none to 18 millirad.

From these considerations it is believed that radiation effects deleterious to patients are not to be expected from I-132 tracers as stated.

TABLE 3

CALCULATION OF WHOLE BODY RADIATION DOSE PER UNIT CONCENTRATIONS OF I-132 (compared briefly with I-131)

Radiation Dose	*I-131*	*I-132*	*Ratio I-132/I-131*
First day $\frac{\text{rad/day}}{\mu\text{c/gm}}$	20.5	10.35	1/2
Total $\frac{\text{rad}}{\mu\text{c/gm}}$	247	10.35	1/24

(Since I-131 and I-132 are isotopes of the same element, equal tissue concentrations (C) are to be expected. To obtain the dose value for any tissue except thyroid where isotope concentration (C = μc/gm) is known, simply multiply by the appropriate constant listed above.)

DISCUSSION

The data reported here suggest that a simple, practical method is available for the distribution of a short half-life isotope of iodine at a great distance from the pile source. This device is easy to transport, offers no problems of either installing or "milking," and has a useful life of several weeks. The solution is easily obtained by simple manipulations within the ability of most technicians. The I-132 content shows stability of composition and predictability of specific activity. Contamination is negligible. The generator is, therefore, both easy and safe to use.

Radiation calculations based on known and theoretical situations suggest that reasonable radiation doses to an organism are delivered under the conditions stated. The distinct advantage compared to I-131 is that less radiation to the organism by a significant factor (1/24) occurs. For humans the peculiar merit of this isotope lies in the possibility of repetitive testing at short intervals of time which may be possible because of the short half-life and the lowered radiation dose. A few uses of I-132 which appear promising are: repetitive patient testing at short time intervals (i.e. 24 hours); synthesizing doubly tagged compounds, where preparation time is short; and testing thyroid function in the presence of therapeutic doses of I-131.

Some disadvantages of I-132 are its short half-life and high energy gamma. Any procedure involving a lengthy time period causes significant decrease in the amount of isotope available and may result in insufficient isotope to count accurately. The high energy gammas may produce collimating problems and require increased shielding. This may make some procedures such as scanning more difficult. At present this isotope is also more expensive than I-131.

SUMMARY

1. Evaluation of the new Brookhaven National Laboratory Generator for the production of iodine^{132} indicates it to be a simple and safe unit for general use.

2. The I-132 solution obtained from the generator is free of significant radioactive and chemical contamination by direct tests.

3. Radiation calculations for internal administration in humans suggest that I-132 reduces the radiation exposure by a significant amount as compared to I-131.

"The author gratefully appreciates the technical assistance of Louise Overton and Dolores Kenyon."

APPENDIX

Whole Body Dose Calculation for I-132:

Dose (gamma): $D = C\ g\ (1.44\ t\ I\gamma \times 10^{-3})$
$D = (200\ C)\ (1.44 \times 2.33 \times 9.6 \times 10^{-3})$
$D = 6.44\ C$ rad

Dose (beta): $D_B = (C)\ (73.7\ \bar{E}_B T)$
$D_B = (C)\ (73.7 \times 0.53 \times 0.1) = 3.91\ (C)$ rad

Total dose: $D + D_B = 10.35\ (C)$ rad

First day and total dose are the same for I-132 due to short half-life.

Whole Body Dose Calculations for I-131:

$D = C \times 200 \times (1.44 \times 192 \times 2.33 \times 10^{-3}) = 123\ C$ rad
$D_B = C \times 73.7 \times 0.21 \times 8.0 = 124\ C$ rad

Total Dose: $= D_B + D = 247\ C$ rad

First day dose: $= f_d \times D_T = 0.083 \times 247 = 20.5\ C$ rad

N.B. Because a smaller geometry factor, g, applies, the gamma dose to the thyroid is smaller than the whole body gamma dose. Thus, the total dose to the thyroid of I-132 is:

$D = C\ (17.6) \times 1.44 \times 2.33 \times 9.6 \times 10^{-8} = 0.58\ C$ rad
$D_B = C \times 73.7 \times 0.53 \times 0.1 = 3.92\ C$ rad

Total = 4.50 C rad

Similarly, the total dose to the thyroid for I-131 is 132 C rad. (The rad used in these calculations is defined as 100 ergs/gram of tissue).

C = Tissue concentration of isotope (μc/gm
g = geometrical factor
$I\gamma$ = dose rate (rad/hr) at 1 cm in air from an unfiltered point source of 1 mc
$\bar{E}_B$ = the average energy per disintegration of the beta rays in MEV
T = isotope half-life in days
1.44 X t = average life of isotope in hours.

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Control of Radiation Quality and Field Size at the Treatment Port of the Medical Research Reactor[1,2,3]

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One of the principal reasons for constructing the Brookhaven Medical Research Reactor (MRR) (1) was to obtain a device which could provide a flux of slow neutrons in the emergent beam higher than had been available from the larger Graphite Research Reactor. Since, in the experimental therapy program, patients are exposed to this emergent neutron beam, it is even more important than usual to do everything possible to insure its quality and purity, consistent with achieving the required high fluxes. It is also, of course, necessary to confine the neutron beam and to restrict it as much as possible to the area which it is desired to irradiate, while sparing other areas from irradiation. The problem of controlling the radiation quality and field size at the treatment port may be considered under two main topics: 1) Limiting the slow neutrons to the desired area, and 2) Eliminating the fast neutrons and gamma rays. Before considering either of these topics in detail, however, it may be helpful to consider the general configuration of the MRR. As is shown in the cutaway drawing of Fig. 1, the central reactor core, which contains the uranium fuel elements and which is water-cooled, is surrounded by an air-cooled graphite reflector 3 feet thick. Most of this graphite reflector is in turn surrounded by a biological shield made of heavy concrete. In the path between the reactor core and the treatment port are several modifications, among the most important being the shutter, which in Fig. 1 is shown in the up or open position. In the down or closed position, the pyramidal-shaped opening of the treatment port is replaced by a solid mass of heavy concrete, which shuts off almost all of the radiation from the core. This makes it permissible for personnel to work in the patient treatment room for short periods of time with the reactor operating, for example, to put a patient into position. Some radiation does leak through the shield but, of course, it is also possible to keep the power of the reactor at a low level until the working personnel are safely out of the room, thus minimizing their exposure. Fig. 2 shows

[1]Research supported by the U. S. Atomic Energy Commission.

[2]Medical Research Center, Brookhaven National Laboratory, Upton, L.I., N.Y.

[3]Presented at 7th Annual Meeting, Society of Nuclear Medicine, June 24, 1960.

a vertical section through the core, reflector and open shutter. In order to understand the reasons for first trying to use and later modifying this design, we must review some of the underlying principles which govern the choice of materials and their location.

ELIMINATION OF FAST NEUTRONS AND GAMMA RAYS

Essentially all of the neutrons which eventually emerge from the treatment port originate in the reactor core as fast neutrons. These fast neutrons are best slowed down to the desired energies by collision with materials having low atomic weights and low neutron capture cross sections such as graphite and heavy water. (Natural water would be an even better moderator but has a significant neutron capture cross section.) If a sufficient amount of these materials were interposed between the core and the port, all fast neutrons could be eliminated from the emergent beam, but as the distance from the core increases, the emerg-

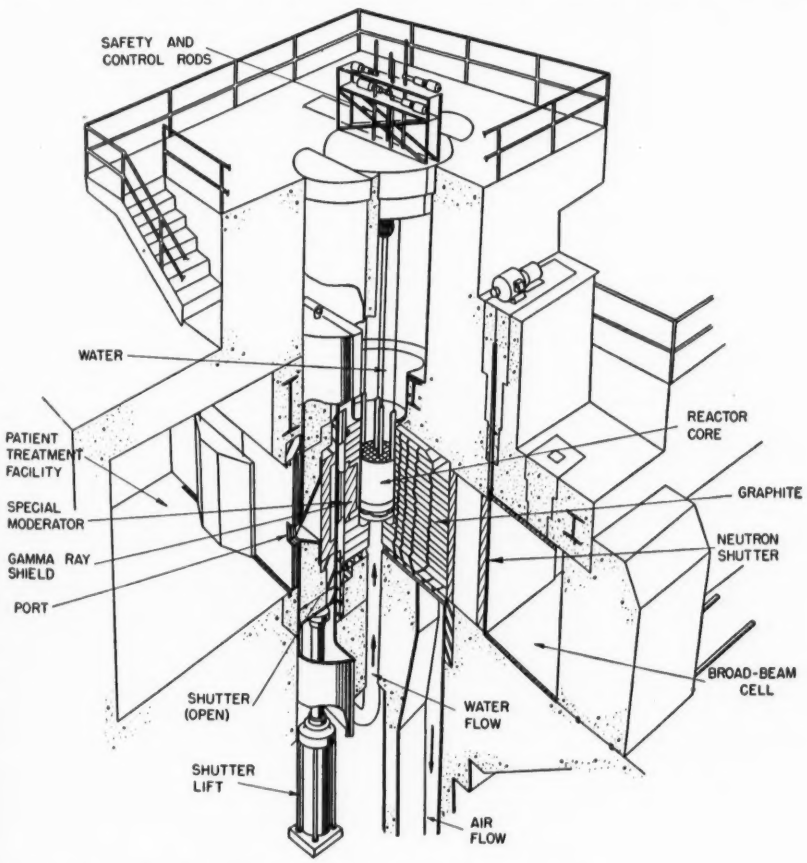

Fig. 1. Cutaway drawing of MRR showing shutter in the open position.

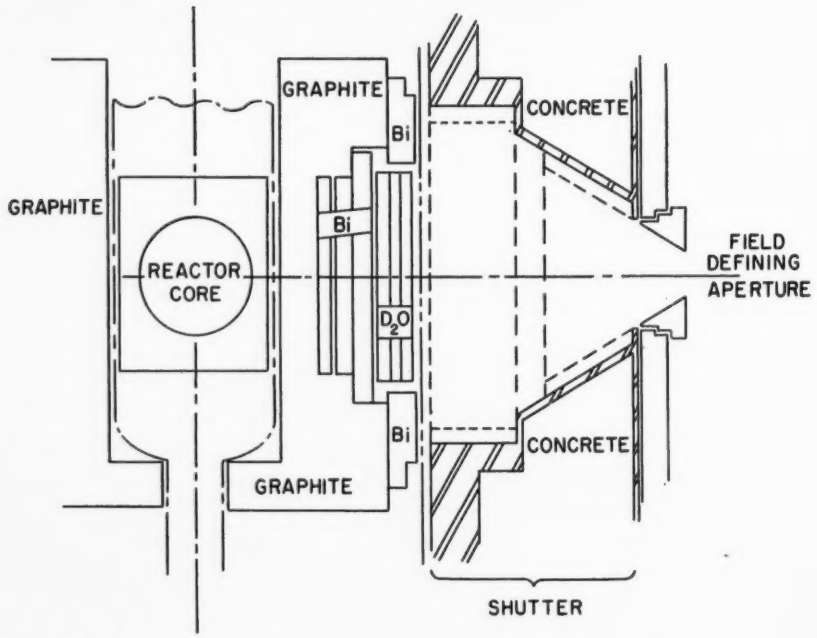

Fig. 2. Detail of core-to-port path.

ent slow neutron flux is decreased by scattering and absorption as well as by geometry. To maximize the emergent slow neutron beam, it is necessary to keep the core-to-port distance as short as possible, so the amount of material which can be interposed is limited. It is, of course, highly undesirable to have materials which capture neutrons in the core-to-port path, as this process not only removes neutrons from the beam but adds gamma rays. Outside of the core-to-port path, neutron-capturing materials are relied upon to shield out the neutrons.

Gamma rays originate not only from the fission process in the core but also from neutron capture reactions in the reflector and in the shield. It is especially undesirable to permit many neutrons to enter the heavy concrete shield, as in the reaction with iron in the concrete, highly penetrating 5 MeV gamma rays are generated. Some gamma rays, about which nothing can be done, also originate from neutron capture reactions in the tumor and in normal tissues exposed to the neutron beam. Whereas moderation of the fast neutrons to slow neutrons requires low atomic weight elements, the linear stopping power of materials for gamma rays depends chiefly upon their density, and thus the high atomic weight elements constitute the best shielding materials. No single material is very good for both purposes and combinations of high and low "Z" elements are needed. Bismuth is one of the best materials for gamma shielding in a reactor because of its high density and its high transparency to neutrons. The bismuth located as shown in Fig. 2 effectively stops the core gammas but does not remove the

gamma rays which originate in the shield. One of the major alternations which has been made in the shutter since the original configuration was tried was to move much of the bismuth from the location shown to a new location at the port end of the shutter. It is best to have some bismuth in both locations. Too much bismuth near the port adds to the neutron-scattering problem. Another change has been to move the heavy water container into the shutter.

CONFINING THE SLOW NEUTRONS

The pyramidal opening in the shutter in Fig. 2 is designed to let the port "see" as large an area of the reflector (the effective source of slow neutrons) as possible and at the same time to prevent neutrons from escaping into the shield. To the latter end, the channel is lined with a two-inch thick layer of polyethylene backed up by a layer of Boral. The plastic liner serves to reflect neutrons back

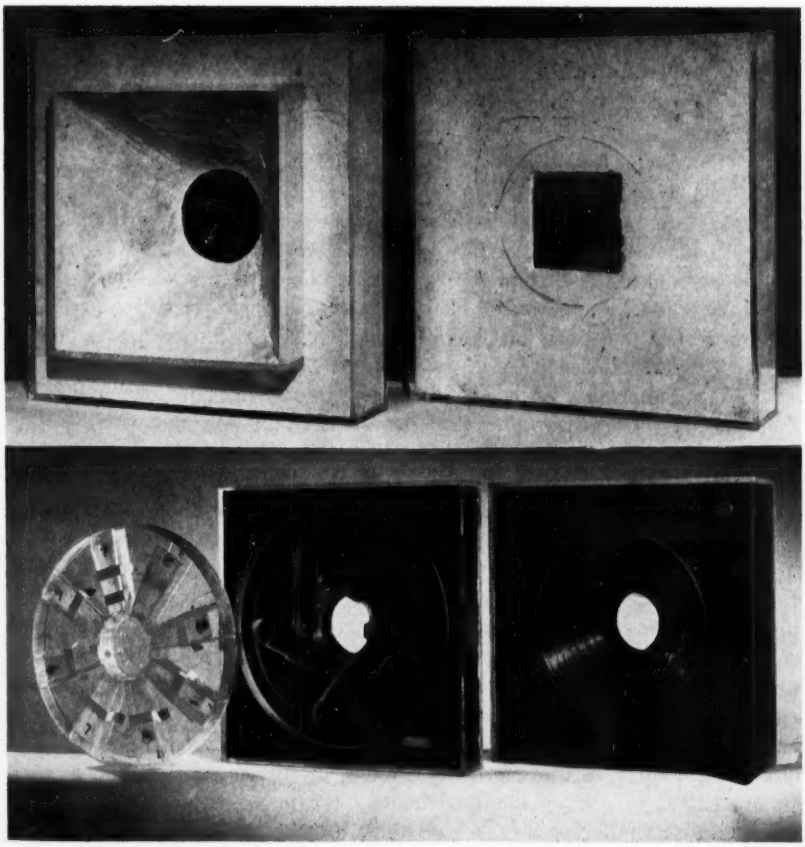

Fig. 3. (Top) Paraffin-lithium aperture blocks used for final shaping of the neutron beam.
Fig. 4. (Bottom) Device for holding mice for partial body irradiation at treatment port.

into the channel. Studies of its effectiveness indicate that the presence of the plastic liner contributes a factor of two to the emergent slow neutron flux. Some gamma rays are generated by the reaction with hydrogen in the plastic, but there is a net gain in the neutron-to-gamma ratio.

Materials which capture slow neutrons are used to limit the field of the therapeutic irradiation. For this purpose, the required nuclear properties are a high neutron capture or absorption cross section and a minimum of unwanted ancillary radiations related to the capture process. Atom-for-atom, the naturally-occurring mixture of boron isotopes is over ten times as effective as natural lithium. In each case, one isotope is responsible for the greater part of the effect, and in comparing these isotopes we find that boron-10 is about four times as efficient as lithium-6. The B^{10} reaction has the disadvantage of being accompanied in 93 per cent of the events by an 0.4 MeV gamma ray emitted from the excited form of Li^{7} which is one of the two heavy particles produced. Within the shield this relatively low energy gamma is not a serious problem, as it is subsequently absorbed. Also, boron is obtainable in forms such as Boral which are safer and easier to handle than any form of lithium which has been tried. Neutrons which penetrate through the plastic liner are largely prevented from entering the concrete by a Boral layer, thus avoiding the generation of 5 MeV gammas by neutron capture in the shield.

For the final field-defining aperture, a removable block consisting of LiF in paraffin is used. This block is shown in more detail in Fig. 3, which shows a block with a round opening as seen from inside of the shutter and another with a square opening as seen from the treatment room. At this location, Li is preferred over boron as a neutron absorber because lithium does not emit a gamma in its neutron capture reaction as boron does. It is also interesting to note that because of its greater density, a given volume of LiF contains more Li than does the same volume of pure Li metal. This is not true for LiF powder, which packs rather loosely, but does apply to LiF suspended in paraffin and would apply to fused LiF. The use of Pb-Li alloys has been suggested but not as yet tried in this reactor. Certainly the suspension of Li in paraffin is not an ideal solution to the problem because of the gamma rays created by reactions with the hydrogen in the paraffin. A special block designed to hold mice and selectively to irradiate implanted muscle tumors is shown in Fig. 4. For added protection of certain areas, sheets of Li metal are placed locally as shown in Fig. 5. The lithium surface is coated with mineral oil and contained in a plastic bag when so used. Enriched Li^{6} is especially useful here, as a given thickness is several times as effective a neutron shield as is the case for natural lithium, and a thin sheet is desired for fitting it to body surfaces. The depression of the neutron flux on the lithium-shielded side relative to the other side is to be noted. It is also important to realize, as this illustration shows, that a piece of lithium so placed does not cast a very deep neutron shadow; the neutrons which go around it readily diffuse into the shadow.

With the present configuration, a slow neutron flux of 2×10^{10} n/cm^2•sec per megawatt of reactor power is achieved at the port, and the reactor has been

operated at power levels up to 5 MW for brief intervals of time. The beam is essentially free from fast neutrons, although some of intermediate energy remain, the cadmium ratio being about 40. (The cadmium ratio was obtained by activating gold foils in pairs simultaneously. In each pair, one foil was covered with aluminum, the other with cadmium, which shields the foil from thermal neutrons. The ratio of the activities induced is used as an index of the thermalization of the neutrons.) The present gamma ray intensity is 0.6 r/MW•sec. It is very difficult to reduce the gamma ray dose rate any further as nearly everything which is done

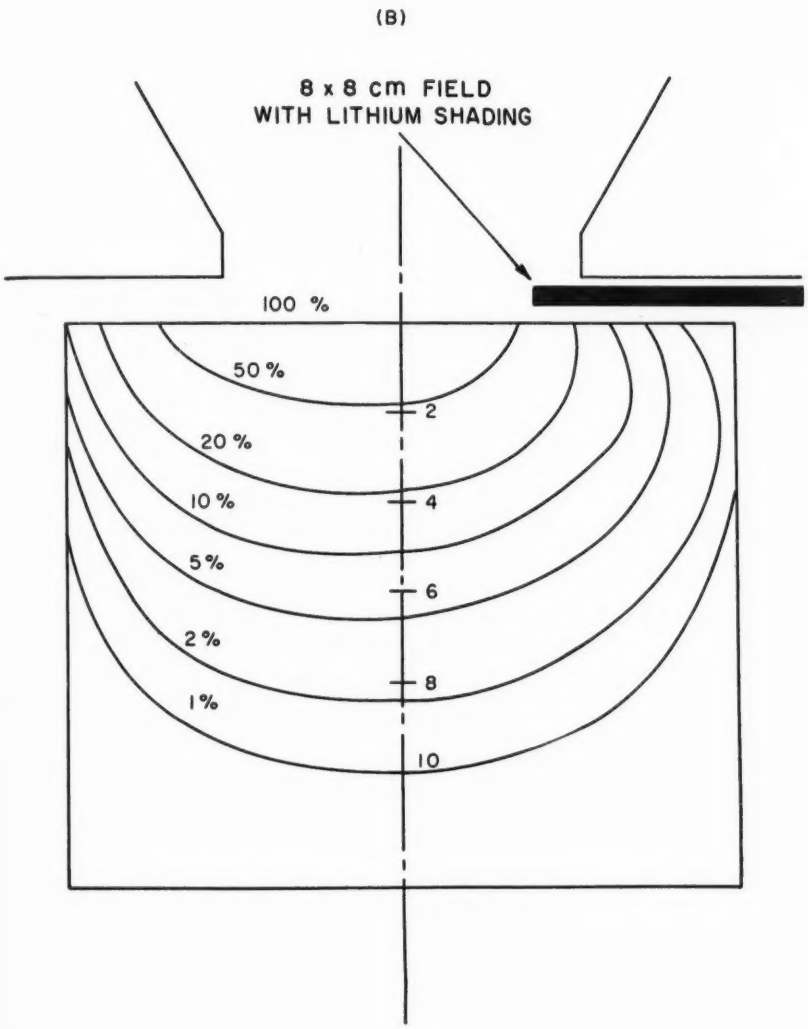

Fig. 5. Effect of depth in tissue and of lithium shielding upon neutron flux.

to stop the gamma rays or to prevent their formation costs a proportional reduction in the slow neutron flux. It may be necessary to go to an entirely different mode of operation, such as the use of a flash reactor, to overcome the remaining difficulties. One attractive new idea which has been suggested by the AMF Atomics Division of the American Machine and Foundry Company is called SYFTOR, for "*Syn*chroscreened *F*ast Reac*tor*." In this device the usual limitations imposed by the interposition of selective absorbers and moderators between the core and the target are overcome by taking advantage of the fact that the diffusion time for thermal neutrons is appreciably longer (several milliseconds for an 80-cm path) than the time required for fast neutrons and gamma rays to travel the same distance. This is achieved by using a flash reactor with a moving shield, with the movement synchronized with the flash so that the shield is in the beam path at the time of the flash and absorbs the prompt radiation gammas and fast neutrons, then moves out of the beam path while the thermal neutrons leak out of the core tank. These and other ideas are under active consideration. Finally, we may say that the Medical Research Reactor is not to be regarded as having a final design, but that further development of the reactor itself must accompany further progress in the use of the reactor in the treatment of human disease.

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Detection of the Small Left-to-Right Intracardiac Shunt With Methyl Iodide I-131[1]

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INTRODUCTION

Successful detection of the small left-to-right intracardiac shunt has been accomplished by using Methyl Iodide I-131 as an indicator. The early appearance of radio-activity in the right heart following inhalation and solution of this gas in the pulmonary capillary blood forms the basis for this determination. The work of Amplatz has been confirmed and this procedure has proved sufficiently simple and accurate for use in a general hospital (1).

Ludes, using peripheral arterial blood sampling, first employed a radioactive substance, ethyl iodide, in the detection of circulatory shunts (2). Thode used the inhalation of methyl iodide to obtain accurate left heart injection of an indicator avoiding predilution in the right heart and pulmonary vascular bed to study left heart hemodynamics (3). Morrow, sampling right heart blood, utilized the gas nitrous oxide as an indicator in the detection of left-to-right intracardiac shunts (4). Case confirmed the work of Ludes (2) and applied the technique of Morrow (4), using ethyl iodide I-131 (5). Simultaneously Sanders reported the same method of shunt detection, using Krypton-85. Amplatz reported the use of methyl iodide I-131 as an indicator, thus simplifying the technique by using an indicator gas which was readily available, easily administered and detected (1). The method of Amplatz was employed in this present work.

MATERIALS AND METHODS

Methyl iodide I-131 is delivered to the lungs by inhalation and the early appearance of radio-activity in the right heart is sought to establish the presence of a left-to-right shunt.

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Fig. 1. Reagents used in preparation of methyl iodide I-131 showing commercially available sterile saline, stable methyl iodide, and sodium iodide I-131.

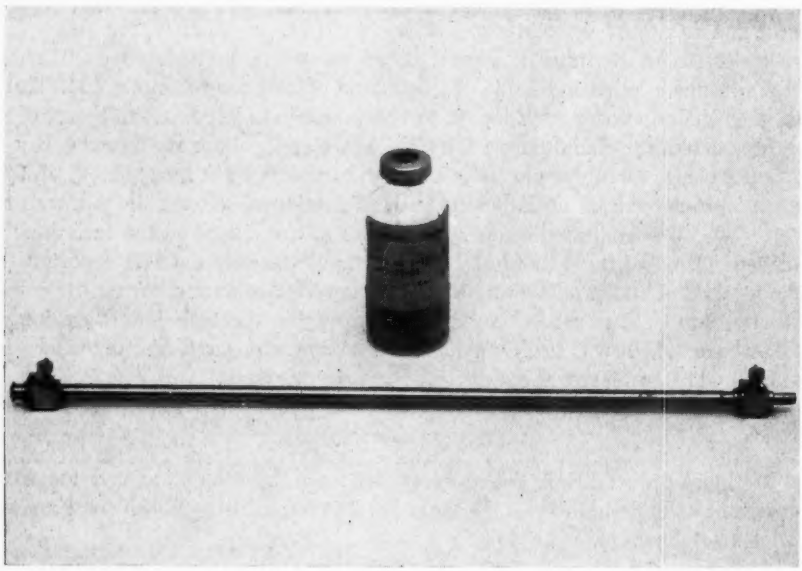

Fig. 2. Methyl iodide I-131 generator and stainless steel tube.

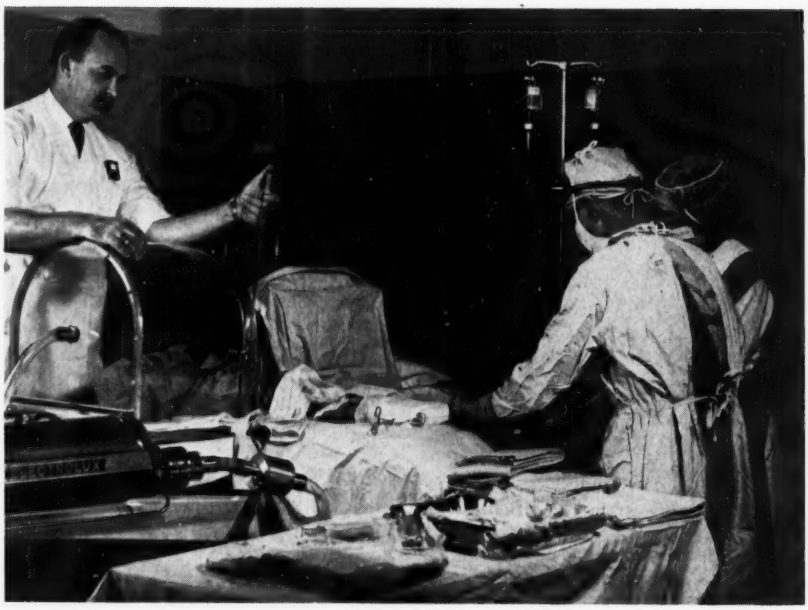

Fig. 3. Physical arrangement of the patient, the plastic hood, the stainless steel tube, the evacuation pump, the filter system and cardiac catheter.

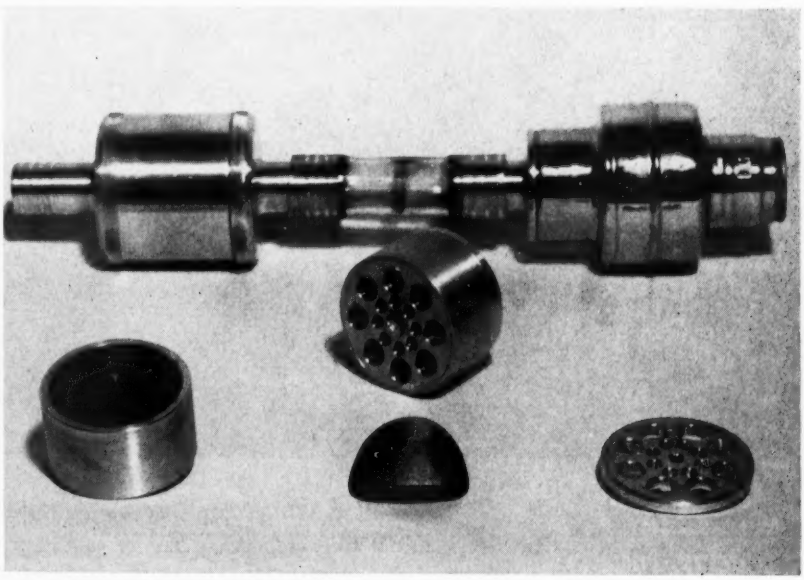

Fig. 4. Filter system showing breakdown of the main unit.

Methyl iodide is a yellow liquid having the following characteristics: Density, 2.28 at 20°C, boiling point 42.5°C, vapor pressure 331.4 mm Hg at 20°C and 483 mm Hg at 30°C. Water solubility is 1.4 grams per liter at 25°C.

Toxicity studies performed by Thode (3) using plain methyl iodide demonstrated that inhalation of 400 mg of the gas produced no detectable change in chickens or rabbits. After breathing 4.5 grams, death occurred in 6 hours, from pulmonary edema. This is far in excess of the infinitesmal amount, approximately 1 mg, used in this procedure.

Methyl iodide I-131 is obtained through a simple exchange reaction with methyl iodide and sodium iodide I-131 equilibrated in aqueous solution. Three millicuries of sodium iodide I-131 in aqueous solution is placed in a 30 cc multiple-dose rubber sealed bottle containing 14.5 cc water and 3 drops of methyl iodide (Fig. 1).

This is allowed to equilibrate at 78°F for 24 hours. The container is stored in the "hot lab." The gas collected from this source has an activity of 5 microcuries per cubic milliliter.

Prior to the test, the gas is collected in a special 4 cc stainless steel tube closed on each end with a regular B-D one-way clip type stopcock. (Fig. 2).

Using the present procedure, approximately 97 per cent of the gas in the tube is delivered to the oropharynx. Approximately 30 per cent of the total gas

Fig. 5. Well counter.

delivered remains in the tracheobronchial tree, depending on its solubility in water, and 20 per cent is removed by the pulmonary capillary blood from the lung in 3 seconds (1,3). The first and second exhalations following the administration of the gas contain methyl iodide I-131.

Prior to the test the patient is given Lugol's solution to load the thyroid. The test is performed in a plastic hood. The indicator is administered during inhalation. The radio-active methyl iodide gas is delivered to the oropharynx through a sterile 5 French 15-inch Pharmaseal premature infant feeding tube, during inspiration, by displacement with a 10 cc syringe. Simultaneous sampling of the right heart blood is accomplished by withdrawal of timed 1-cc-volume samples through the cardiac catheter. The plastic hood is constantly evacuated through an activated carbon filter system during, and for three minutes following, the administration of the gas. Figures 3 and 4.

The delivery tube and the filters are counted prior to and following the administration of the gas. The tubes, containing 1-cc samples, are counted in a scintillation well counter (Fig. 5).

CATHETER POSITION	O_2 SATURATION	PRESSURE	MEAN
Femoral Artery	96%	110/56	74
Pulmonary Capillary	100%	16/6	9
Pulmonary Artery	72%	19/6	12
Rt. Ventricle	73%	24/5	
Rt. Atrium	73%	6/0	4
Superior Vena Cava	69%		
Inferior Vena Cava	85%		

2·14·61

Fig. 6. Catheterization data, Case 1.

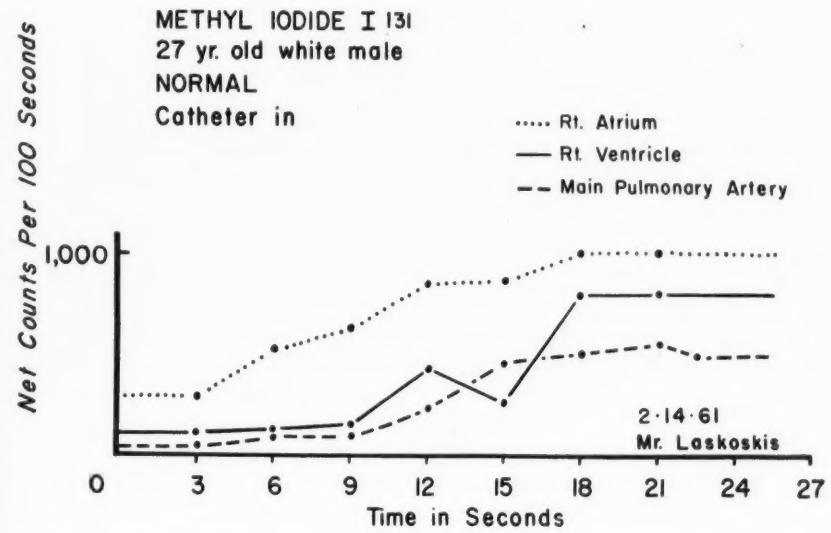

Fig. 7. Methyl iodide curves, Case 1.

Fig. 8. Chest roentgenogram, Case 2.

The early appearance of radio-activity in the pulmonary artery indicates the presence of a left-to-right shunt, either proximal to or at this site. The anatomic location of the shunt is found by systematically withdrawing the catheter to the right ventricle, right atrium and the vena cavae, and repeating the procedure at each site. The most proximal site revealing early appearance of the radio-activity indicates the location of a single lesion or the most proximal portion of a complex lesion.

Following administration of methyl iodide I-131, radio-activity normally appears in the right heart at 12 to 16 seconds. In the presence of a left-to-right shunt the appearance time in the pulmonary artery is less than 5 seconds.

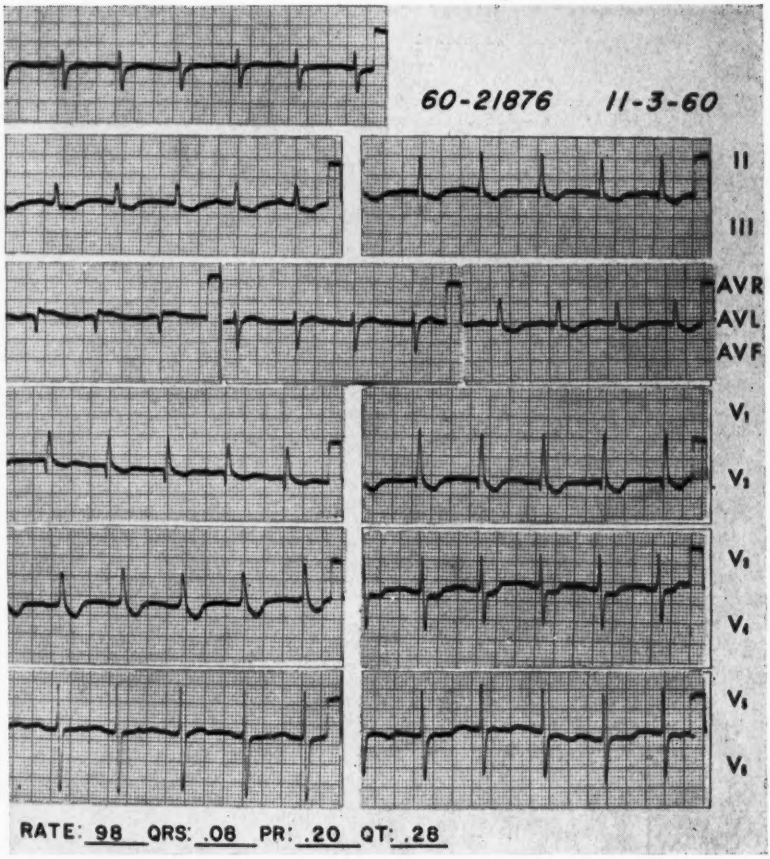

Fig. 9. Electrocardiogram, Case 2.

CASE PRESENTATIONS

Case 1. A 27-year-old white male with no evidence of cardiac shunt was examined in the laboratory. The patient had a normal appearance time in the main pulmonary artery, right ventricle and right atrium. Figs. 6 and 7.

Case 2. An acyanotic 45-year-old white female was examined, who gave a history of frequent upper respiratory infections, dyspnea of two years duration, fatigue for one year, and hoarseness for two months. The physical findings were consistent with an atrial septal defect specifically showing enlargement of the heart to the left, right ventricular thrust, Grade 3 systolic murmur at the pulmonary area, widely split and fixed second heart sound with the pulmonary component greater than that of the aortic. The roentgenogram revealed enlargement of the right ventricular outflow tract, marked enlargement of the pulmonary arteries and hypervascular lung fields (Fig. 8).

CATHETER POSITION	O_2 SATURATION	PRESSURE	MEAN
Rt. Femoral Artery	96%	130/75	
Superior Vena Cava	66%		
Inferior Vena Cava	71%		
Rt. Atrium			
mid	80%	15/0	4
low, above tricuspid	82%		
Rt. Ventricle			
low	84%	75/-10	
outflow below the pulmonary valve	81%		
Main Pulmonary Artery	81%	64/30	
Rt. Pulmonary Artery	81%	60/30	37
Rt. Pulmonary Capillary	no sample	5/0	5
Lf. Atrium	96%	18/-5	

CHARACTERISTIC – resting - room air – no anaesthesia 9·27·60

Fig. 10. Catheterization data, Case 2.

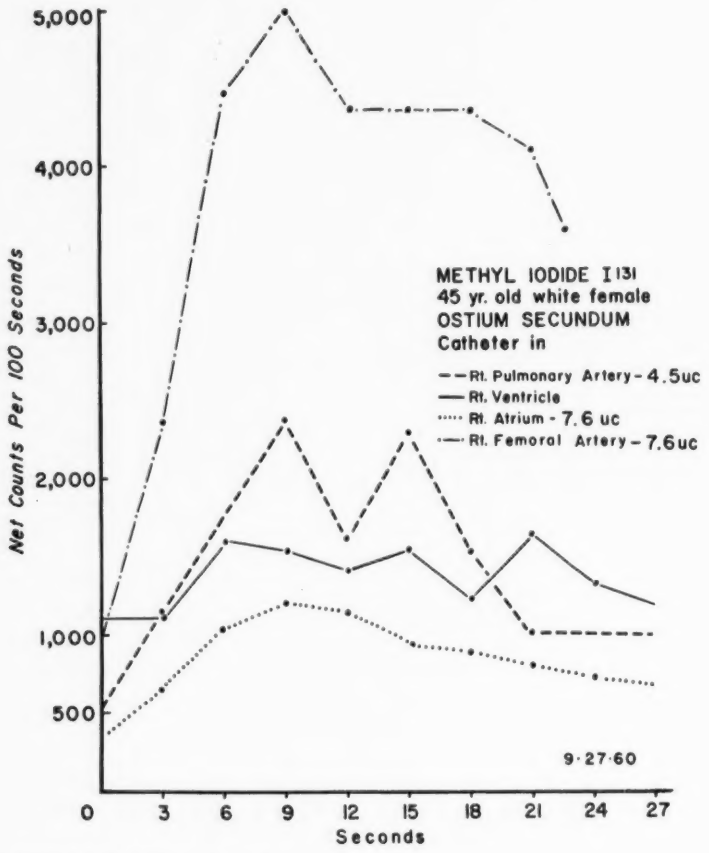

Fig. 11. Methyl iodide curves, Case 2.

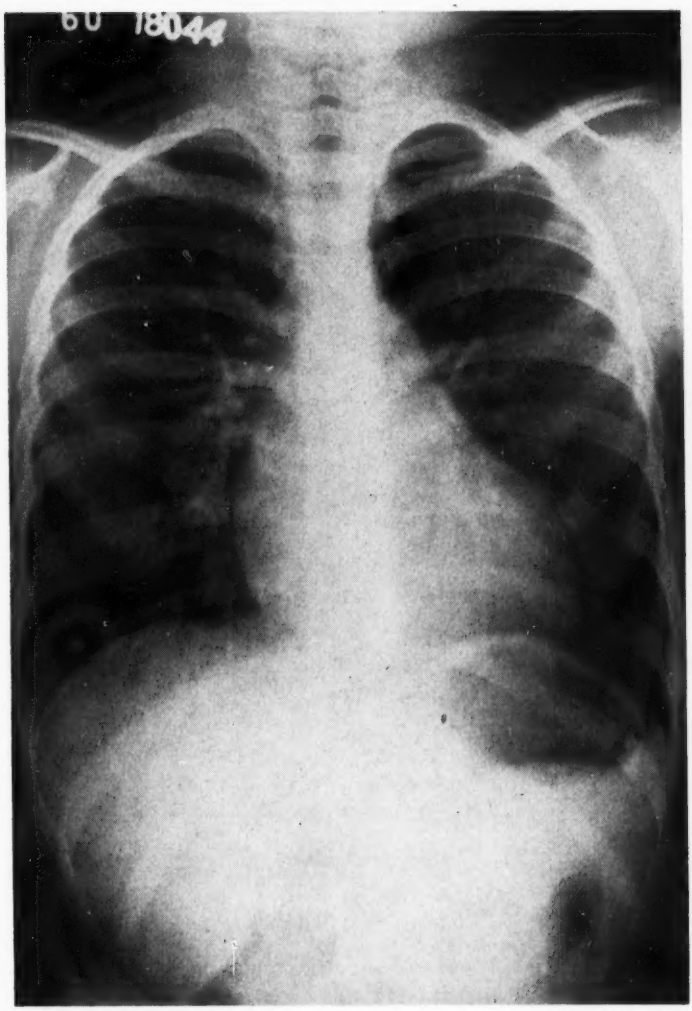

Fig. 12. Chest roentgenogram, Case 3.

The electrocardiogram revealed a clockwise loop, right ventricular hypertrophy and strain (Fig. 9).

The catheterization data revealed a significant oxygen gradient in the right atrium (Fig. 10).

The methyl iodide curves confirmed a left-to-right shunt at the atrial level (Fig. 11).

At surgery a large 2.5 cm secundum defect was found and closed by atriopexy.

Case 3. An acyanotic 10-year-old white female presented with a history of repeated upper respiratory infections and a heart murmur present at birth. The

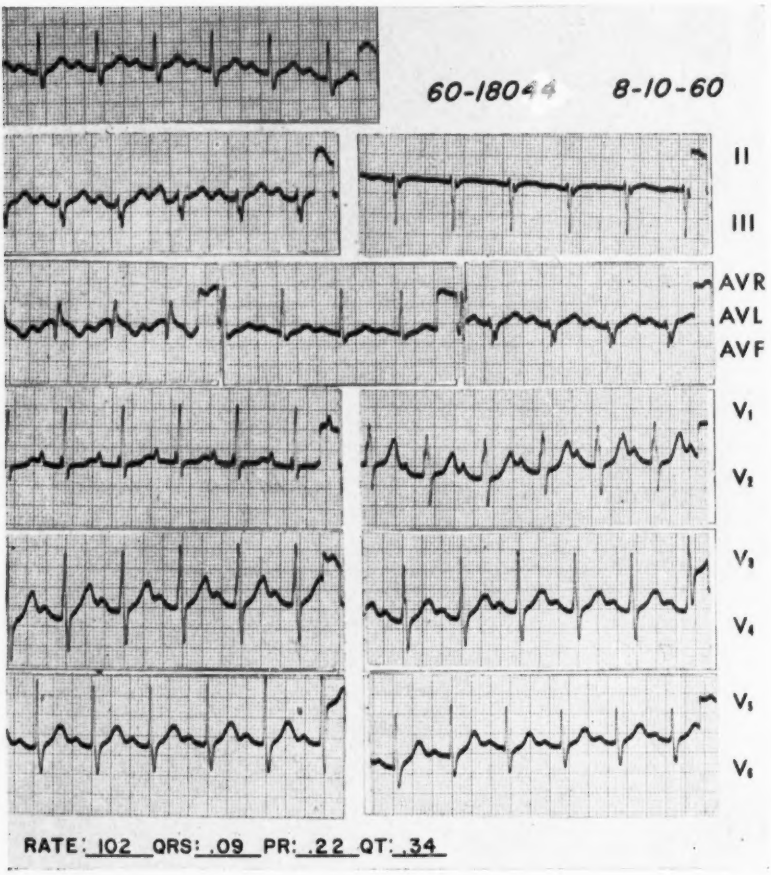

Fig. 13. Electrocardiogram, Case 3.

physical findings were consistent with an atrial septal defect specifically showing a right ventricular thrust, widely split and fixed second heart sound but complicated by a Grade 3 holo-systolic murmur in the third left intercostal space at the left sternal border. The roentgenogram revealed enlargement of the outflow portion of the right ventricle and increased vascularity of the lung fields (Fig. 12). The electrocardiogram revealed sinus rhythm, prolongation of the PR interval, S_1, S_2, S_3 syndrome and right ventricular hypertrophy, with a counter-clockwise loop (Fig. 13).

The catheterization data revealed a significant oxygen gradient in the right atrium (Fig. 14).

The methyl iodide curve revealed a left-to-right shunt at the atrial level (Fig. 15).

At surgery an endocardial cushion anomaly was found, including a primum defect of the atrial septum and a high ventricular defect with intact atrioventricular valves. The defect was closed with a prosthesis.

CATHETER POSITION	O_2 SATURATION	PRESSURE	MEAN
1. Rt. Femoral Artery		106/60	74
2. Rt. Pulmonary Capillary	98%	10/4	6
3. Rt. Pulmonary Artery Near Capillary	86.5%	20/10	16
4. Aorta	96%	89/58	
5. Left Ventricle at Aortic Valve	95%	86/9	
6. Left Ventricle in Aortic Valve	96%		
7. Left Ventricle at Mitral Valve	95%		
8. Left Atrium at Mitral Valve	95.5%	7/2	
9. Rt. Atrium at Defect	85%		
10. Rt. Atrium at Tricuspid Valve	86%		
11. Mid Rt. Atrium	78%	5/1	
12. High Rt. Atrium	70%		
13. Rt. Pulmonary Artery	86%	35/15	
14. Main Pulmonary Artery	86%	35/15	
15. Pulmonary Artery at Pulmonary Valve	88%		
16. Rt. Ventricle at Pulmonary Valve	88%	35/5	
17. Rt. Ventricle below Tri Valve	90%		
18. Rt. Atrium at SVC	70%		
19. Rt. Atrium at IVC	70%		
20. Superior Vena Cava	66%		

Fig. 14. Catheterization data, Case 3.

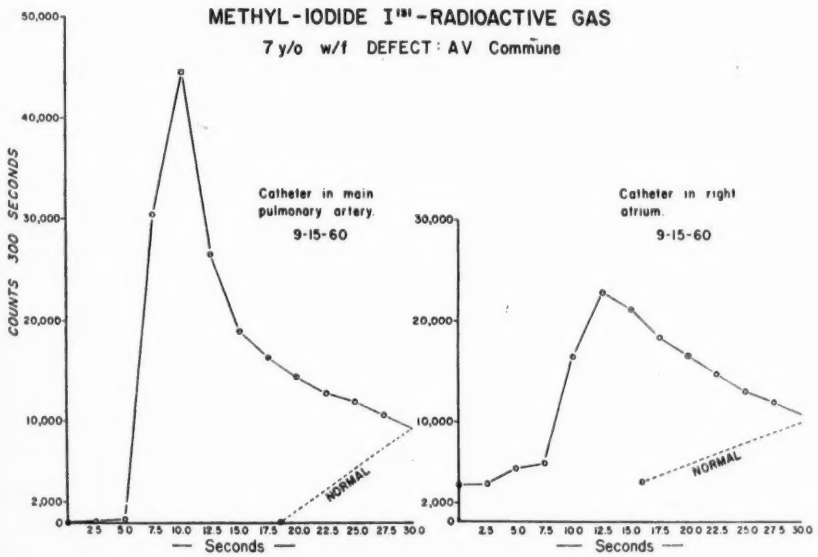

Fig. 15. Methyl iodide curves, Case 3.

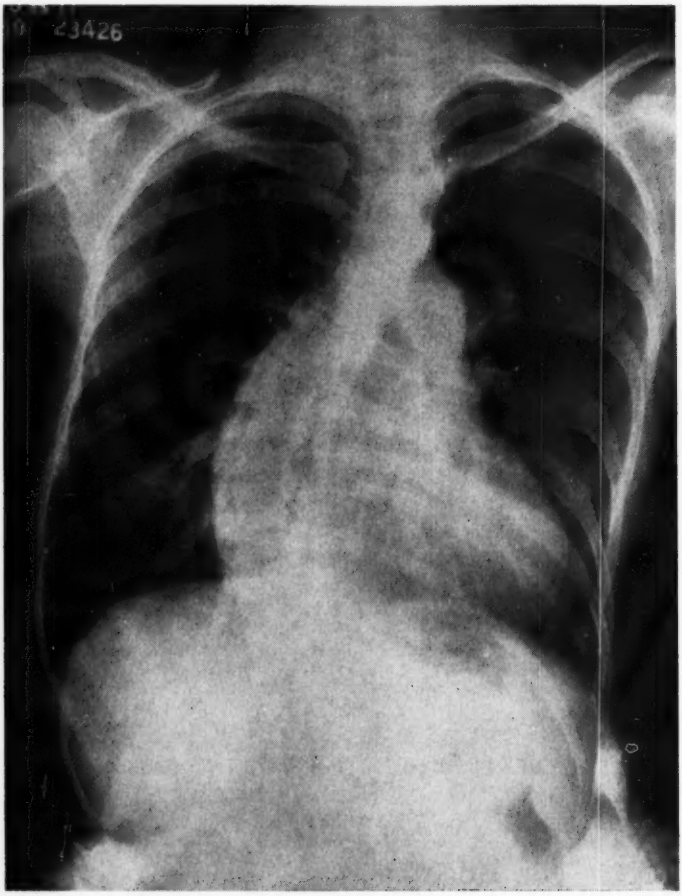

Fig. 16. Chest roentgenogram, Case 4.

CATHETER POSITION	O_2 SATURATION	PRESSURE	MEAN
Femoral Artery	96 %	130/75	92
Main Pulmonary Artery	76 %	14/7	9
Infundibular Area	76 %	11/2	
Rt. Vent	78 %	80/2	30
Rt. Atrium	76 %		

10·12·60

Fig. 17. Electrocardiogram, Case 4.

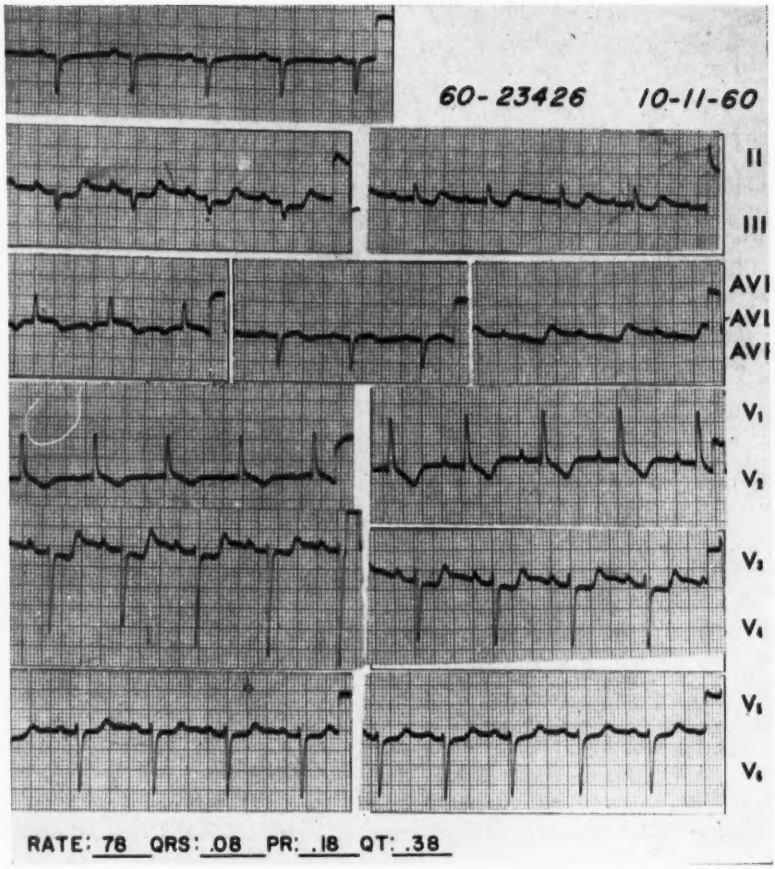

Fig. 18. Catheterization data, preoperatively, Case 4.

Case 4. An acyanotic 36-year-old white female with kyphoscoliosis presented with a life-long history of a heart murmur. Dyspnea and paroxysmal tachcardia had been present intermittently for nine months. Physical examination was consistent with pulmonary stenosis specifically showing a right ventricular thrust, a systolic Grade 4 ejection murmur at the left sternal border in the second intercostal space, and a diminished single second heart sound. The roentgenogram revealed enlargement of the right ventricle and decreased vascularity of the lung fields (Fig. 16).

The electrocardiogram revealed prolongation of the PR interval, right axis deviation, right ventricular hypertrophy and strain, and right atrial enlargement (Fig. 17).

The catheterization data revealed a pressure gradient at the pulmonary valve without abnormal oxygen gradient (Fig. 18).

The methyl iodide curve revealed a left-to-right shunt at the atrial level (Fig. 19).

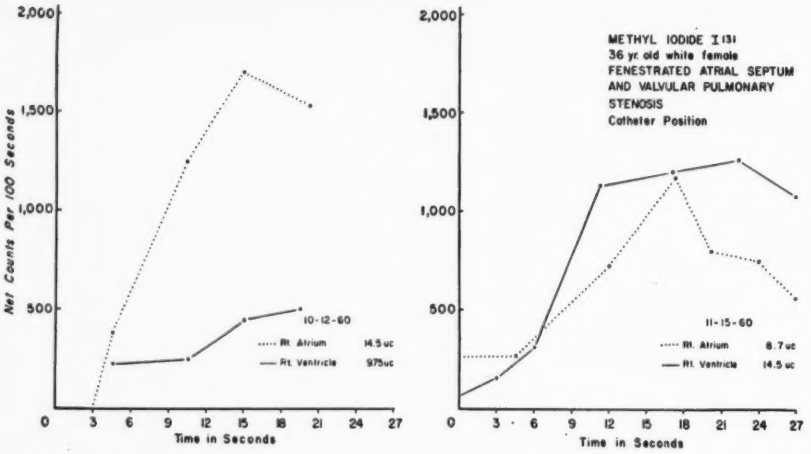

Fig. 19. (A) Methyl iodide curves preoperatively, Case 4.
(B) Methyl iodide curves, postoperatively, Case 4.

CATHETER POSITION	O2 SATURATION	PRESSURE	MEAN
Femoral Artery	95%	140/65	80
Rt. Pulmonary Artery	83%	28/5	
Rt. Ventricle	83%	65/0	23
Rt. Atrium			
high	84%	4/0	
mid	84%	4/0	
low	84%	4/0	
Superior Vena Cava	76%		
Pulmonary Vein	96%	10/0	5
Left Atrium	96%	8/-2	

11-15-60

Fig. 20. Catheterization data, postoperatively, Case 4.

There was no oxygen gradient to substantiate the shunt. The fidelity of the I-131 method indicating a shunt was not appreciated. The results were ignored and pulmonary valvulotomy was performed, following which the patient developed a persistent tachycardia of 120 per minute and orthopnea which was progressive. Physical examination revealed a hyperdynamic right ventricular thrust, Grade 4 systolic ejection murmur at the pulmonary area, Grade 1 short diastolic murmur of pulmonary insufficiency and increased single heart sound at the base. When the patient was re-catheterized the data revealed a definite oxygen gradient at the atrial level (Fig. 20).

Repeat methyl iodide curves revealed the same pattern of left-to-right shunt as before (Figure 19 B).

At surgery the atrial septum was fenestrated with multiple separate defects; these were repaired.

DISCUSSION

The fidelity of the methyl iodide I-131 inhalation method of left-to-right shunt detection in the study of congenital heart lesions is obvious. In the last case methyl iodide I-131 indicated a left-to-right shunt when no oxygen gradient at the time of the initial study was observed. The oxygen gradient in the right heart may show a shunt of the magnitude twenty-five percent of the cardiac output (9). The dye dilution technique with two catheters may show a left-to-right shunt as small as ten percent of the pulmonary flow (10). Methyl iodide as the radioactive gaseous indicator is more sensitive than either of these two methods (1).

SUMMARY

The inhalation technique with methyl iodide I-131 has proved to be useful in the study of congenital heart disease manifesting left-to-right shunt because of its simplicity and fidelity.

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Measurement of the Mean Transit Time of Cerebral Circulation by External Detection of an Intravenously Injected Radioisotope[2]

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INTRODUCTION

One problem particularly suited to radioisotope techniques is the safe measurement of cerebral circulation in the human. Applications of isotopes to measurements of cerebral circulation have been reviewed by Greitz (1) and more recently by Fazio and Fieschi (2). The techniques described in the literature largely involve direct injection or sampling following direct carotid arterial or jugular venous puncture. Substitution of radioactive gases for tests utilizing the Fick principle (3) has made accurate gas analysis simpler. The work of Reinmuth (4) combines external detection and jugular sampling to measure brain circulation.

Other than the work of Eichhorn (5), Ljunggren (10), Love (6) and Thompson (7) all of these techniques require cannulation of neck veins and, at times, arterial punctures. Although valuable information can be gained by such approaches, neck vessel puncture, in addition to being hazardous, places the patient in an unphysiological state, requires considerable cooperation of the patient, and precludes frequent repetition of testing. These factors caused a shift in our interest to external measurement of gamma-emitting isotopes circulating through the brain. The location of the cranium away from other body areas renders it particularly suited to isolation by external collimation-detection. This factor also applies, of course, to any study of gamma-emitters in the brain and this advantage probably will be much more widely exploited in future brain research. We shall also, of course, detect radioisotopes present in meninges, bone, and scalp. In the

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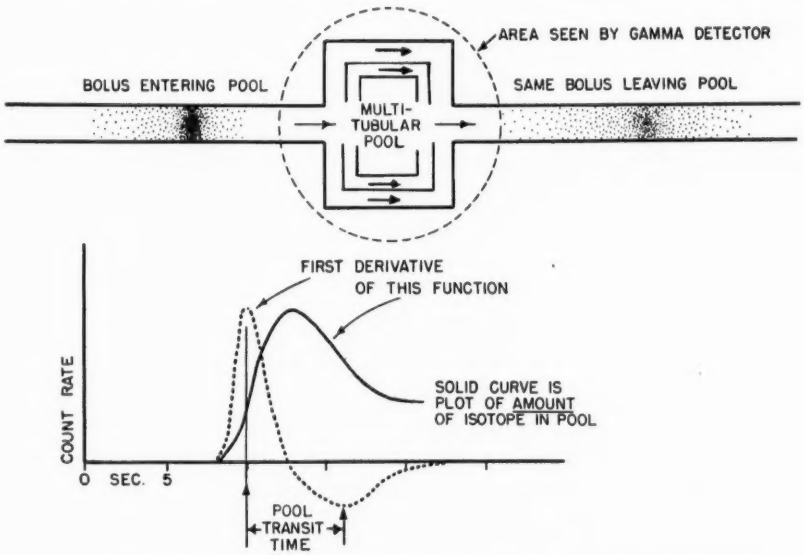
present study we have, of necessity, ignored the contribution from these tissues. The contribution of the scalp has been studied (6) and, although detectable, is probably insignificant when seen against a background of the highly vascular brain. Fazio and Fieschi (2) have studied the radioactivity evident in the cranial region of the head after common carotid injection in the presence of a known internal carotid occlusion. The isotope detected was quite insignificant.

With these thoughts in mind, we sought to find out how much clinically useful information might be derived from the external monitoring of a circulating bolus of radioisotope after an antecubital intravenous injection. If useful, such testing might have great clinical value because of its atraumatic nature and simplicity. Some of the earlier work using this approach has already been presented. (12, 13, 14) This article is intended to bring up to date our thinking on the subject.

To be clinically useful a test to measure cerebral circulation should be very safe, simple to administer, repeatable, painless, and accurate. It should also


AREA SEEN BY GAMMA DETECTOR
BOLUS ENTERING POOL
SAME BOLUS LEAVING POOL
MULTI-TUBULAR POOL
FIRST DERIVATIVE OF THIS FUNCTION
SOLID CURVE IS PLOT OF AMOUNT OF ISOTOPE IN POOL
COUNT RATE
0 SEC. 5
POOL TRANSIT TIME

BASIC PRINCIPLE OF A METHOD OF MEASURING THE TRANSIT TIME OF A RADIOACTIVE BOLUS THROUGH A POOL BY EXTERNAL GAMMA RAY DETECTION

Fig. 1. The estimation of circulation time of the cranial blood pool is based upon timing the interval between the entrance of the most radioactive portion of the intravenously injected bolus and its exit from the pool. These reference points are determined by noting the point of maximum increase and the point of maximum decrease of the isotope content of the pool as the bolus passes through. This is most easily done by differentiating the curve representing the amount of isotope in the pool as a function of time. The interval between the positive and negative peaks of this first derivative then represents the mean transit time of the densest portion of the bolus. It is important to note the spread of distribution of the bolus induced by its transit through the multitubular cranial pool.

ideally give information which will reflect moment-to-moment changes in circulation rather than an average value for a prolonged period. Unfortunately no such technique exists.

PROCEDURE

Our approach has been to produce, following antecubital venipuncture, a bolus which remains as sharply demarcated as possible. The ultimate passage of this bolus through the intracranial blood pool, after heart and lung transit, is monitored by external collimated detectors. With our technique we have attempted to isolate each hemisphere, as well as can be easily done, by developing a dual collimation system which simultaneously monitors each hemisphere. We have tried to define the mean transit time of the cerebral blood pool by the principle diagrammed in Figure 1. As described previously (13) this method, as carried out with our collimation-detection system, also defines the volume of flow to one hemisphere relative to the other.

We might logically discuss the various aspects of the test by isolating several factors important in the measurement.

The bolus. For our purpose we wish to deliver the isotope into the right

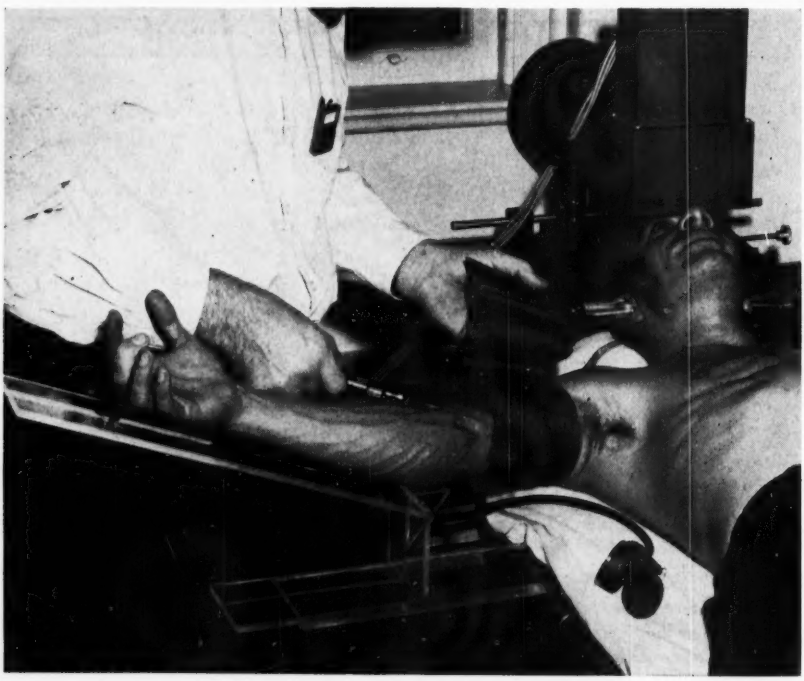


Fig. 2. The arrangement of physician, subject, arm, blood pressure cuff, and armboard immediately prior to release of the bolus. The venous pressure in the arm at this time is approximately systolic arterial pressure. There is no circulation in the arm distal to the cuff.

heart in the shortest possible time. The technique we use consists of placing the patient in a prone position with the head placed in the detection-collimation unit shown in Figure 2. A special armboard (shown in Figure 2) is used which supports the arm in a somewhat elevated position with support only at the elbow. The elbow is bent slightly but not enough to hinder antecubital venipuncture. The middle finger of the supinated forearm holds onto a ring in the distal end of the support. A "velcro"[1] blood pressure cuff is placed on the arm exhibiting the most prominent antecubital veins. The cuff is inflated to 10-20 mm. below systolic pressure for 1-2 minutes. During this time a venipuncture with a 21 gauge needle is performed. After the vein is cleanly punctured and the needle is lying in the lumen, the cuff is inflated above systolic pressure to completely isolate from the general circulation the circulation of the arm distal to the cuff. Approximately 400 microcuries of hippuran—sodium ortho-I^{131} iodohippurate—(we use Hipputope-Squibb) is injected into the vein. The actual rate of injection is unimportant but it need not be rapid. This gentle injection precludes the occasional slippage of needle from syringe with its attendant contam-

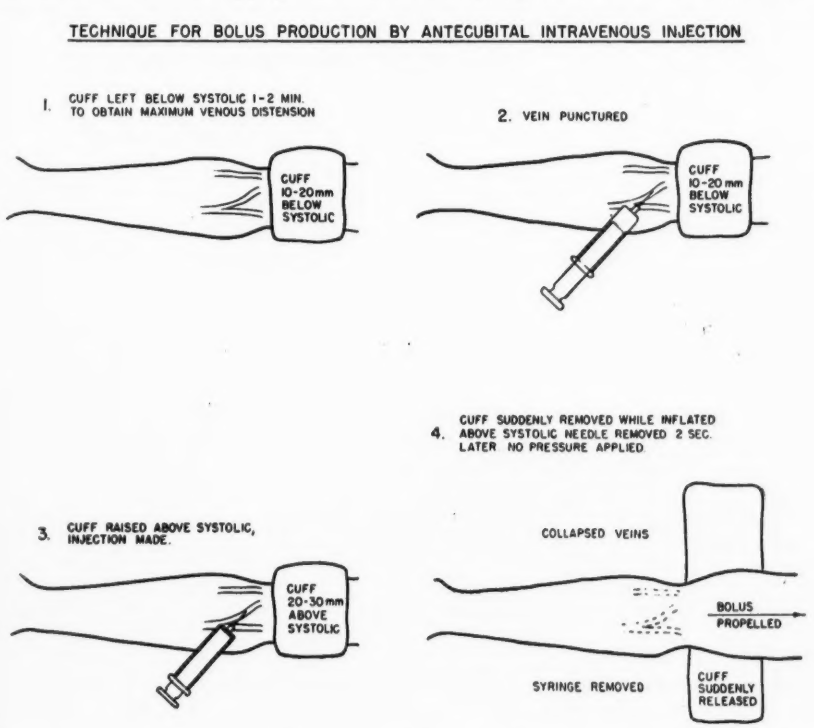

TECHNIQUE FOR BOLUS PRODUCTION BY ANTECUBITAL INTRAVENOUS INJECTION
1. CUFF LEFT BELOW SYSTOLIC 1-2 MIN. TO OBTAIN MAXIMUM VENOUS DISTENSION
CUFF 10-20mm BELOW SYSTOLIC
2. VEIN PUNCTURED
CUFF 10-20 mm BELOW SYSTOLIC
3. CUFF RAISED ABOVE SYSTOLIC, INJECTION MADE.
CUFF 20-30mm ABOVE SYSTOLIC
4. CUFF SUDDENLY REMOVED WHILE INFLATED ABOVE SYSTOLIC NEEDLE REMOVED 2 SEC. LATER NO PRESSURE APPLIED
COLLAPSED VEINS
BOLUS PROPELLED
SYRINGE REMOVED
CUFF SUDDENLY RELEASED

Fig. 3. Showing the sequence of events producing a well-demarcated bolus by peripheral intravenous injection. It is important that the arm be supported in a manner allowing free drainage after cuff release.

[1]Available from the Taylor Instrument Co., Rochester, New York.

ination of the room. When all is ready and the actual test is desired, the cuff is ripped off fully inflated. The arm proximal to the elbow is held by the armboard well above any support so that the cuff may fall completely free of the arm when released. This minimizes any delay in venous drainage. All of the curves shown were done with this general technique but the only curve using the special armboard is shown in Figure 8. Curves done with this armboard show a bolus seeming to be definitely sharper than with a simple, flat, arm support. As soon as the veins have clearly collapsed (about 1-2 seconds after release) the needle is removed and no pressure is applied to the injection site. The technique is graphically shown in Figure 3.

Five to nine seconds after release the isotope begins to appear in the cranium and the plot of the amount of isotope begins to rise. By this time the needle has been out of the patient about 5 seconds and he is in no discomfort as the actual test period begins some 12 seconds after cuff release.

About 5 seconds after the leading edge of the streamed-out bolus arrives in the brain, the densest (most radioactive) portion of the bolus arrives in the brain blood pool and the curve rises most rapidly. See Figure 5. The maximum height to which the plot of the amount of isotope in the pool rises is very complex and involves several variables. These include the proportion of the bolus

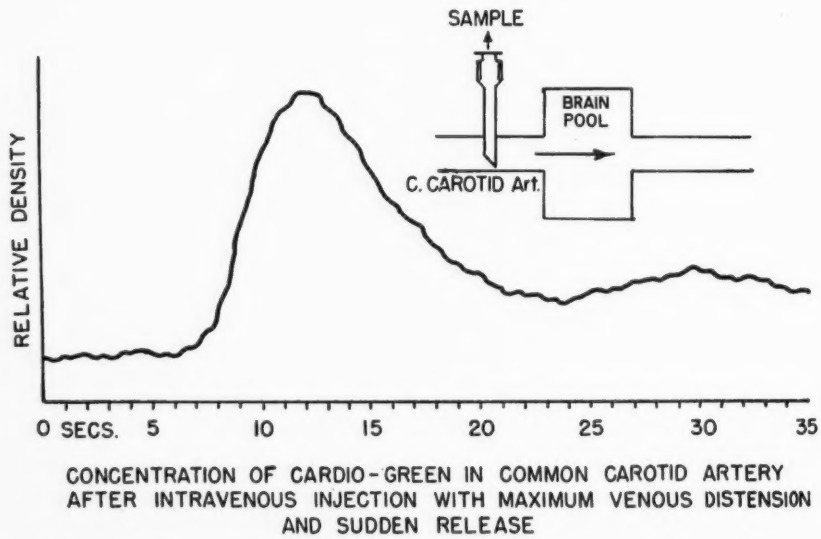

SAMPLE
BRAIN POOL
C. CAROTID Art.
RELATIVE DENSITY
0 SECS. 5 10 15 20 25 30 35
CONCENTRATION OF CARDIO-GREEN IN COMMON CAROTID ARTERY
AFTER INTRAVENOUS INJECTION WITH MAXIMUM VENOUS DISTENSION
AND SUDDEN RELEASE

Fig. 4. A needle has been placed in the common carotid artery and a blood sample is slowly drawn from the needle. It is run through a commercial spectral densitometer which plots the concentration of cardio-green in the vessel. This is shown here to indicate the "shape" of a bolus injected by our technique as the bolus enters the brain. The 5 second interval between the arrival of the leading edge and the densest part of the bolus is typical of our injections. Note the duration of entrance is considerably longer than one cranial pool transit time so that all of the isotope is not in the pool at any one time.

leaving the heart which reaches the cranial pool, the brain blood flow rate, and the duration of entrance of isotope into the pool. The unpredictability of the first of these variables precludes any quantitative flow measurements based upon the area of the cranial curve, such as suggested by Thompson. (7) A theoretical discussion of flow measurement limitations and possibilities has been presented by Cassen. (18) A direct plot of a bolus of cardiogreen sampled from the common carotid by this injection technique (Figure 4) suggests that the region of highest concentration of indicator follows the leading edge of the bolus by about 5 seconds and the entire bolus has entered the head in about 12 seconds. Thus the actual physical length of the bolus as it comes up the neck vessels is of the order of one to two meters. It will be evident that, if the bolus takes about 12 seconds to enter and the usual normal transit time is about 8 seconds, all of the bolus will not be in the pool at any one time.

The curve drops as the isotope empties from the pool and the maximum rate of drop, we believe, signals the time of exit of the densest portion of the bolus.

By simple capacitance differentiation we have directly plotted the slope of the curve representing the amount of isotope in the pool. See Figure 1. Here we are plotting the rate of change of isotope content of the pool. This will be a maximum at the time of entry and a minimum at the time of exit of the most radioactive portion of the bolus. If the times of these positive and negative peaks can be accurately determined we have the means of measuring the mean transit time of this densest portion of the bolus and thus of the blood carrying it. Any recognizable point of reference within the bolus would be suitable for timing entrance and exit from the pool. The densest portion of the bolus is simply the easiest to define.

The interval between the first upward deflection of this derivative curve and the positive peak represents the degree of spread of the bolus between the site of injection and its ultimate arrival in the cranium. This interval defines the time between the pool entrance of the leading edge of the bolus and the entrance of the densest portion of the bolus. With the injection technique described above, this usually will be 4-6 seconds. There is considerable variability of the degree of streaming between arm and head as measured from patient to patient. However, as will be shown, the technique to be described will be affected by this variability only by causing the reference points to be more or less accurately determined.

Curves obtained from four of our presumably normal subjects are shown in Figures 5,6,7,8. It can be seen that the positive deflections of the differential curves are quite well defined and can, in most instances, be estimated to a probable accuracy of 0.5 seconds. The negative peaks are relative ill-defined, however, because the bolus has been considerably shaped and streamed-out by its brain-passage. At present an error of 1-2 seconds is probable. We are certain this accuracy can be improved by steps intended to minimize the high frequency statistical noise apparent in the present tracings and especially conspicuous in Figure 7.

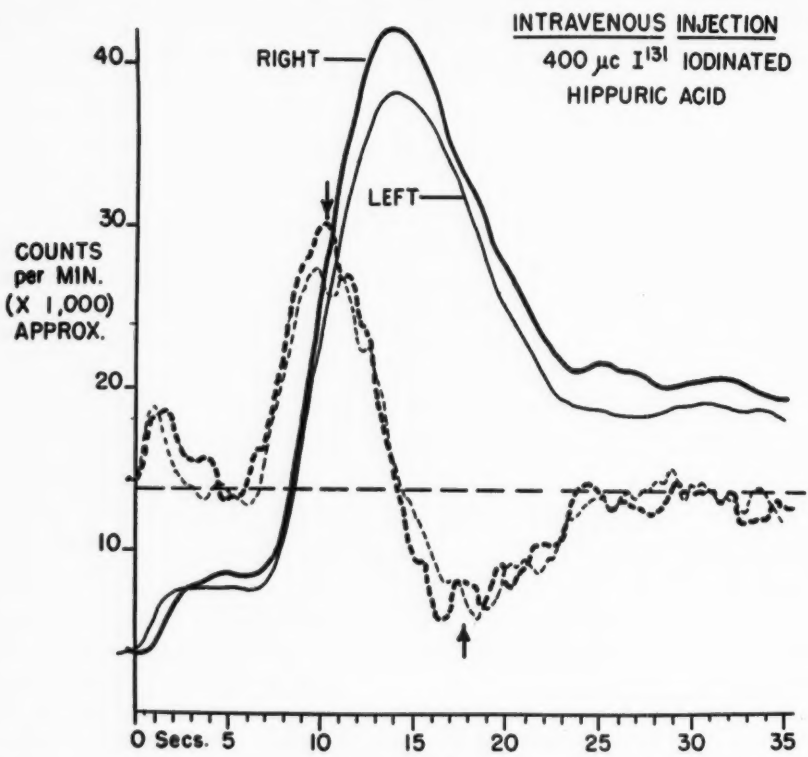


Fig. 5. A normal male, age 33. In this and the following three curves the solid lines represent the amount of isotope in each hemi-cranium. The dashed line represents the first derivative of this function. It shows the rate of change of the pool isotope content. The arrows indicate our visual estimates of the time of occurrence of the peaks. This is the same subject shown in Figure 9.

The broad negative peak indicates that the bolus has been streamed-out by its passage through the brain. Thus the well demarcated, densest portion of the bolus accounting for the sharp, well-defined, positive peak is considerably less well-defined as it leaves. The drop in amount of isotope in the brain is accordingly less abrupt. The extent of this streaming-out as defined by the relationship of the entrance peak to the exit peak might ultimately offer some information about the nature of the vascular bed traversed in the interval between them. Although it is premature to draw any valid conclusions, some of our elderly cases with prolonged transit times have shown rather marked bolus-shaping effects of brain transit.

This streaming-out, bolus-shaping effect of brain passage is well illustrated by Figure 9. This is the same patient as Figure 5. Here a small amount of Hipputope has been injected directly into each common carotid. The amount corresponds roughly to the portion of a 400 microcuries of I^{131} intravenous injection which might be expected to pass through one carotid on the first pass. Here we

may consider the entire amount of isotope is introduced instantaneously into the cranial pool. The positive derivative peak following injection is here influenced by the inability of the servomechanism moving the pens to follow the very rapid initial buildup. The time of injection of the 2cc of solution was less than 0.5 seconds. Despite this rapid injection and buildup of brain activity, the disappearance from the brain is relatively gradual. This presumably is due largely to laminar flow in vessels and multiple circulation times through different regions of the brain. What we see by looking at the entire hemisphere is the aggregate circulation time of the entire brain. There would seem to be, based upon our carotid injections, a considerable range of circulation times for different regions at any one time of testing. It is pertinent, though, that the circulation time defined here is identical to the intravenous curve of Figure 5.

THE FATE OF INTRAVENOUSLY INJECTED HIPPURAN

Our choice of radioisotope was reached out of a desire to use a gamma-emitter which would be very rapidly excreted since we need it for less than 30 seconds after injection. Sodium ortho-I^{131} iodohippurate (hippuran or "Hippu-tope") is particularly rapidly removed from the blood by its complete renal

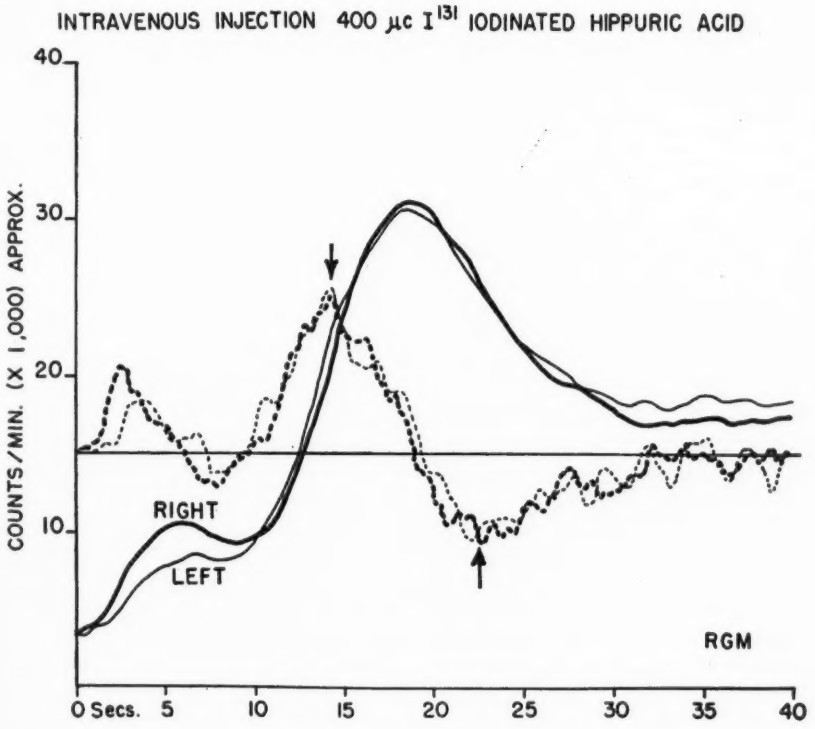


Fig. 6. A normal male, age 46. The negative peak is less obvious than in Figure 5 and the brain circulation time is slightly longer.

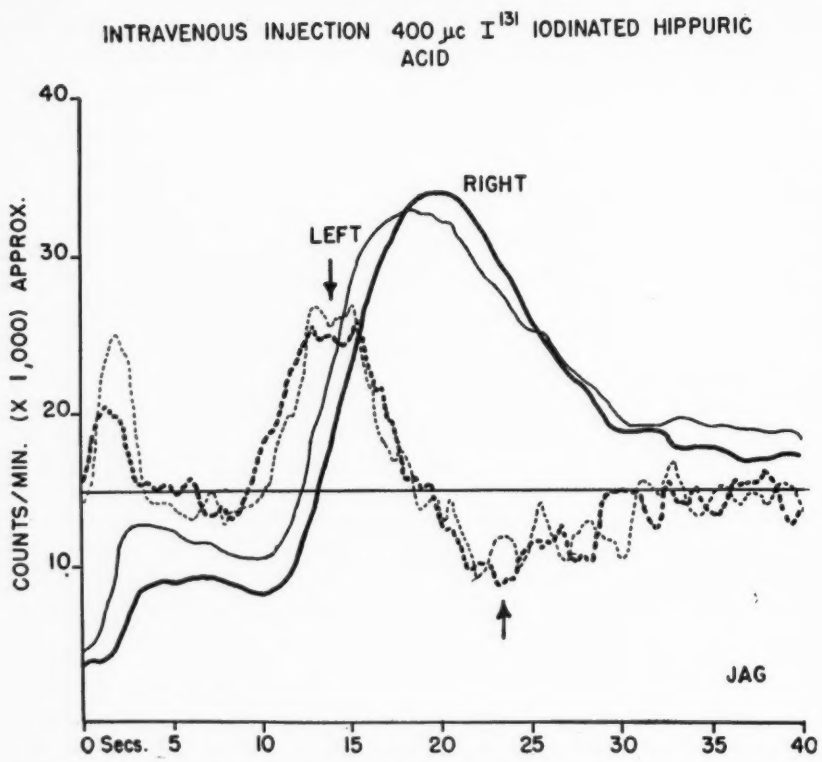


Fig. 7. A normal male, age 46. This curve indicates the handicap created by statistical noise. The interval between peaks is in the region of 9 to 10 seconds but an error of 2 seconds is quite possible.

clearance. (15) I^{131} gamma radiation is of sufficiently high energy to efficiently get out of an object as large as the human head. This chemical form of I^{131} is also appealing because it is readily available commercially with good delivery and at reasonable cost. Because of the rapid renal excretion total body radiation is calculated as less than 5 mr and the kidney and bladder wall at less than 300 mr with a 400 microcurie dose if the patient retains his urine and voids at two hours after injection.

With the knowledge of its complete renal clearance, we thought the brain should be virtually clear of isotope within an hour. However, when we kept a patient in position for one hour after injection and plotted the fall-off of activity in the head we were surprised to note it to be much slower than we anticipated. We then studied three more patients, comparing the amount of activity seen in the head with the blood concentration. Figure 10 is a plot of one study but it is representative of all four cases examined in this way.

It is evident from these studies that the total hippuran content of the brain is not a good representation of the blood concentration. In Figure 10 the blood level is shown as a percentage of the injected 500 microcurie dose in the circu-

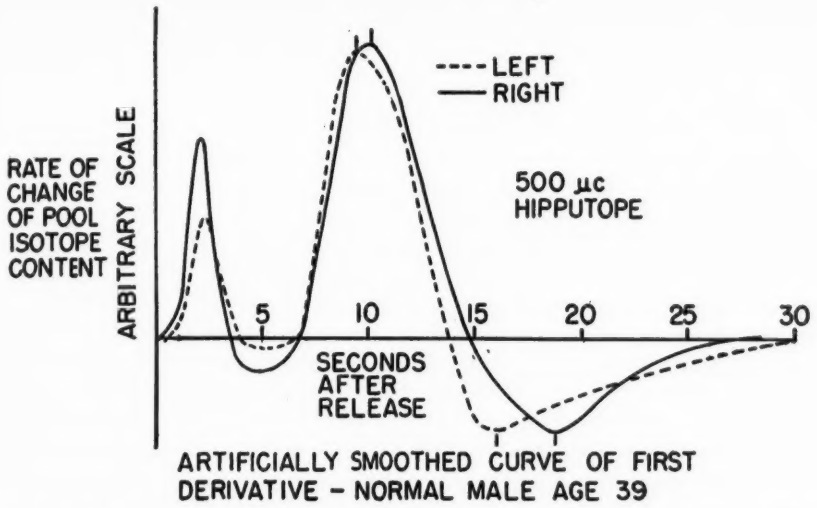


Fig. 8. A first derivative of a study on a normal male. This curve has been artificially smoothed, attempting to show only the low frequency portion of the signal. This curve is the sharpest we have run. We attribute the well-demarcated bolus to the special armboard shown in Figure 2. This is the only case shown here in which this armboard was used. The longer circulation time on the right may represent asymmetrical torcular drainage.

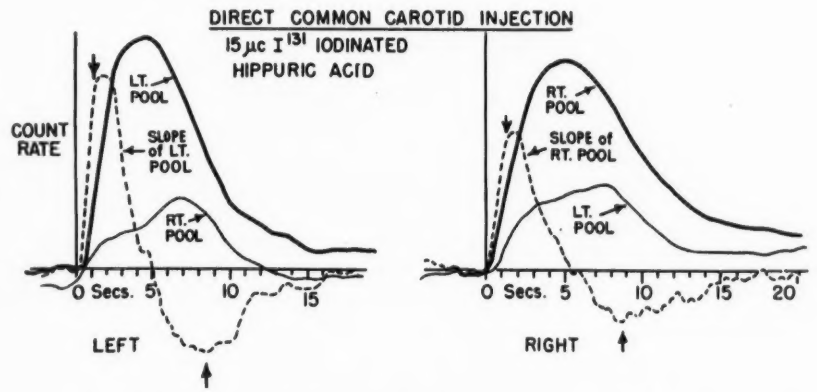


Fig. 9. Same patient as Figure 5. Here 15 microcuries of hippuran have been injected into each common carotid artery. The circulation time obtained by this method is identical, within our limits of measurement, to the intravenous technique. With carotid puncture hematoma formation in the carotid sheath may alter significantly the symmetry of venous drainage. It may also raise the intracranial venous pressure, further modifying the cranial blood pool volume. Note the asymmetry of the solid curves of the isotope content of the pools opposite to the side injected. This suggests that, in this patient, the pool drains mainly to the right since a delayed peak appears on the right after left carotid injection.

lating blood volume. All venous samples were drawn from the arm opposite the injection. Apparently the blood isotope content drops precipitously for the first five minutes. Less than 40 per cent of the injected material is in the circulating blood two minutes after injection as sampled from an antecubital vein. The first two minutes are not plotted here since blood levels during this period are shifting so rapidly that they are not reflected adequately by antecubital sampling. Probably 20-25 per cent of the material is removed by the kidneys on the first bolus renal passage within 20 seconds of the injection.

It will be seen that the fall-off from brain lags considerably behind the blood. This would suggest that some of the material is remaining in some cranial tissue other than the circulating blood. Comparing the difference between the curves it appears that there is a net movement of hippuran into this compartment for about 20 minutes and then a net movement back into the blood thereafter as the blood level drops because of renal clearance. This extravasation probably does not occur rapidly enough to significantly alter our test during the first 25 seconds after injection. Our direct carotid injections (Figure 9) show an almost complete return to the baseline within 20 seconds. This further suggests that significant pickup by brain does not occur during the first half-minute after injection. These studies do suggest, however, that scanning the brain 30 to 60 minutes after hippuran injection might lead to an interesting pattern of its brain distribution relatively free of superimposed blood isotope content. A single 3 cc specimen of cerebrospinal fluid taken 45 minutes after a 500 microcurie injection showed no measurable activity when examined in a commercial well-counter.

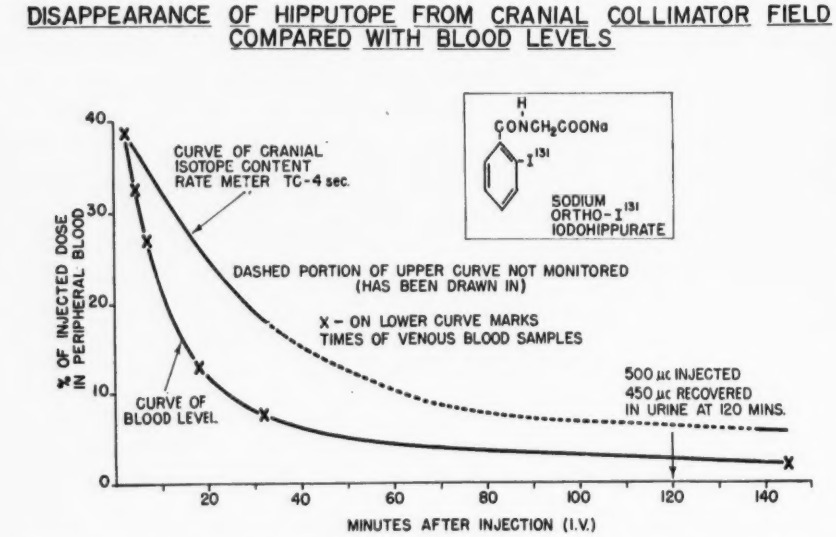


Fig. 10. Two curves indicating the relative rates of disappearance of hippuran from the cranium and blood of a normal male (same patient as Figure 8). As indicated in the text the cranial isotope content is not representative of the blood level. This suggests a small amount is picked up by brain.

Despite this relatively slow disappearance from brain, the isotope content is low enough that no significant interference should result if another test is desired after the first two hours.

INSTRUMENTATION

The head is monitored by a specially constructed collimator and crystal-photomultiplier detectors (Figures 11,12). Reproducible midline positioning is obtained by resting the occiput on a plastic headrest with a shallow "V" configuration with the point of the "V" midline. A transverse bar rests just caudal to the base of the skull.

A specially constructed pair of rounded earplugs move in symmetrically to contact the external ear but are too large to actually enter the external auditory canal. The lower collimator block can be elevated to accommodate smaller heads. The upper collimator block has a midline groove for the nose. Both collimators have 4 cm of lead on the side of the crystals toward the body to limit direct detection of the rather large amount of isotope there.

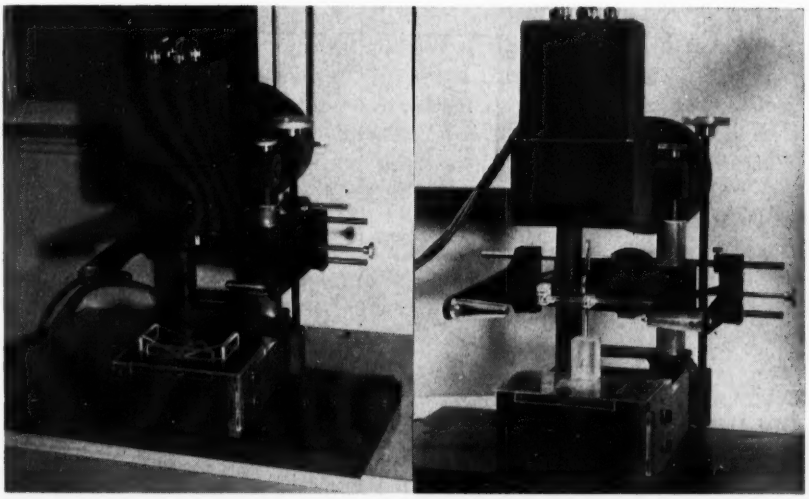


Fig. 11. The head detection unit with the head support in place. The ear-pieces move in symmetrically. Two 1 by 1 inch crystals are in the overhead frontal unit and two in the posterior unit. It was elected to look at each hemisphere from the front and back to isolate each hemisphere and to exclude the much larger amount of isotope in the rest of the body. Such collimation is an expensive luxury since it costs us a great deal of count. However, the possibility of simultaneously measuring the individual hemispheres offers so many clinical research possibilities that this goal has been pursued.

Fig. 12. The head unit with the mock-iodine calibration unit in place. The source is composed of a long half-life radioisotope in amounts simulating the dominant gamma radiation of I^{131}. Two separate sources of 5 and 10 microcuries shown together here may be used individually or together. The support allows them to be swung into either left or right acceptance field.

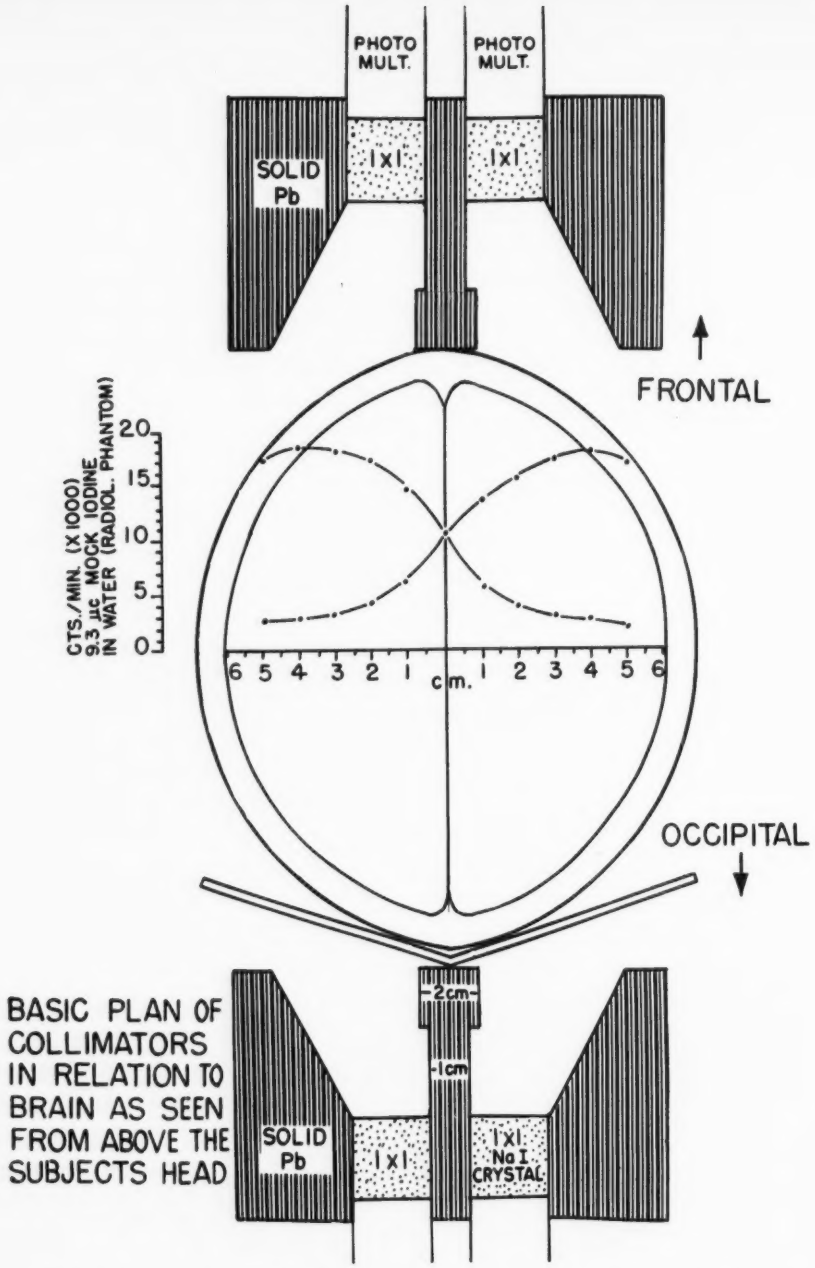


Fig. 13. The acceptance pattern of the collimators tested with a 10 microcurie source in a water-filled Alderson Research Laboratories phantom head. Somewhat better hemisphere separation can be obtained by a higher discriminator setting. However, the resulting rejection of the softer Compton scatter seriously reduces the count rate. The disappointing hemisphere separation encountered with this anterior-posterior collimation has prompted us to undertake a study of the hemisphere lateralization obtainable from the lateral aspect of the hemisphere. Here a considerably more efficient utilization of gamma rays can be made. Limitation of pickup to the ipsilateral hemisphere would then be based upon proximity to the crystal and internal absorption of radiation originating in the opposite hemisphere. Our calculations are not yet experimentally verified.

When hemisphere circulation symmetry is sought, accurate midline position is crucial. The acceptance pattern of each side is cutting off sharply near the midline. Early venous drainage is largely into midline channels. Because of these factors, a slight lateral shift will create a large apparent asymmetry. It remains to be seen how serious a limitation this is on studies of hemisphere symmetry. The asymmetrical and unpredictable drainage of the torcular herophili also may impose further limitations on the usefulness of such studies.

The collimation pattern can be seen in Figure 13. The preamplifier outputs from the right front and back photomultipliers are mixed and fed to one discriminator and rate meter. The left two crystals are similarly connected.

When separation of the hemispheres by this collimator is studied in air, excellent rejection of the opposite hemisphere is obtained. A mockiodine point source 3 cm from the midline (shown in Figure 13) gives a count rate 26 times that of the opposite pair of crystals. In a more pertinent similar measurement in water, this ratio at 3 cm. from the midline is reduced to 5:1, presumably largely as a result of Compton scatter. Somewhat better hemisphere isolation can be achieved by raising the discriminator thresholds to accept only the harder Compton scatter but this results in a further loss of counts in a system already starved for information. A compromise was reached at a 5:1 rejection 3 cm from the midline in a plane midway between front and back collimators. Testing nearer each collimator in water indicates somewhat better separation. The efficiency of counting becomes slightly greater as the frontal or occipital pole is approached but a reasonably homogenous pattern of sensitivity has been achieved by having two detectors "looking" at each other on each side.

The photomultiplier pre-amplifier output is fed to a discriminator circuit contained in a pair of scalers. The pulse is also sent to a rate meter with a time constant of 0.4 seconds. This is, in effect, increased to about 1 second by a subsequent two-stage R-C filter. This network is intended to obtain a sharper cut-off of higher frequency statistical noise components than can be obtained by a single integrating capacitor. Since the rate meter time constant is necessarily short to follow the rapid changes in count rate, noise is a real problem. The direct write-out of the rate meter output looks quite good. This function, however, is differentiated by a simple capacitor (.05 mfd looking into a 0.5 megohm resistive load.) As might be anticipated the resulting derivative appearing across this latter resistor shows a marked accentuation of the higher frequency components. There is probably little useful information in these curves over 0.25 CPS. We are currently incorporating a commercial, dual channel, sharp cut-off low-pass filter in the hope of obtaining a more accurate negative peak resembling those seen in Figure 8. These latter curves were smoothed artificially. We are aiming at obtaining a reliable circulation time with an accuracy of 0.5 seconds. We estimate our present accuracy at plus/minus 1 second. It is quite likely that some direct handling of the pulses by a digital technique would be closer to the ideal.

Two dual channel recording systems are included in the equipment. One pair records the curve of the amount of isotope seen in each hemisphere. The other pair records the first derivative. We may eventually record only the latter since we are coming to feel it contains the most information.

CLINICAL DISCUSSION

Fifteen normal male subjects chosen from our non-neurological patient population have been studied. Circulation times of 6.5 to 10 seconds have been obtained. This is in reasonable agreement with the findings of Nylin and Hedlund,(8) Greitz,(1) and Crandall and Cassen.(11)

DISCUSSION

The blood supply of the brain is obviously of great clinical significance. However, the precise definition of flow volume in the human has suffered severely from the lack of a practical clinical method of measurement. This point is well discussed by Fazio and Fieschi.(2) The first usefully accurate method of measurement that was at all clinically applicable was the nitrous oxide inhalation method of Kety and Schmidt.(16) Although this method gave important basic information it suffered from several handicaps. It required simultaneous arterial and jugular punctures, required prolonged inhalation of a gas, and averaged the brain blood flow over a 10 to 15 minute period. As a result of these factors the test was not widely clinically applicable and tested the patient in an unphysiological state.

Nevertheless the nitrous oxide method and its radioactive gas modifications(3) have been carried out in many research centers. These works not only have given much valuable information but the very performance of the test in the face of its technical complexity attests to the importance attached to the measurement of human cerebral blood flow.

Another approach with much merit is the precise definition of brain hemodynamics by rapid serial carotid angiography.(1) This gives a great deal of information about the distribution of opacified blood in the brain. It is, however, quite expensive and does not lend itself to repeated studies because of this expense, the need for repeated arterial puncture, the chemical effects of contrast medium, the omnipresent hazard of embolization from bubble and clot injection, and radiation limits of the patient's head. Like other studies involving neck vessel cannulation, it is not carried out in a physiological state.

Certainly the most precise measure of brain blood flow is by means of application of electromagnetic flow meters to the carotid and vertebral arteries. Unfortunately this requires surgical exposure of all four vessels and thus is not generally applicable.

Attempts at estimating flow rate by defining the linear rate of progress of the blood stream have, I believe, little place in absolute flow measurements unless there is some way of knowing the effective cross-sectional area of the lumen at the point of measurement. This condition will seldom be met.

Ideally a measurement of brain blood flow will give an absolute quantitative result but the units in which this should be expressed remains unsettled. Flow can be expressed as cc's per minute for the entire brain, cc's per minute per unit volume of brain, or as cc's per minute per unit blood pool volume (expressed

as mean pool circulation time). The inhalation Fick principle tests such as the nitrous oxide and radioactive krypton modifications give results in terms of number of cc's of blood per unit weight of brain tissue per unit time.

The dilution techniques using carotid injection and venous sampling of colored dyes(9) and labeled red cells(8) can express flow in terms of actual blood volume per unit time since, in this situation, we know precisely the amount of indicator going through the pool.

Nylin and Hedlund(8) have also determined the carotid-jugular mean transit time in a large series of patients. Ljunggren *et al* have defined the passage of an intravenously injected bolus up the carotids and back down the jugulars by means of external detectors (10). Crandall and Cassen (11) have studied the carotid-torcular circulation time. Greitz (1) has angiographically studied the brain circulation time in the presence of brain pathology. These works indicate the circulation time to be an index of brain circulation. We are now undertaking a clinical study to evaluate the brain transit time in the presence of known cerebrovascular disease.

If a cranial detection system were calibrated by means of a radioactive standard distributed in a brain phantom the cranial pool blood volume could be calculated by counting the cranium and a blood sample several minutes after a known amount of a non-diffusing isotope was injected intravenously. After obtaining the total blood volume, the brain pool volume could be obtained from the proportion of the total dose present in brain. The per-minute blood volume could then be calculated from the pool volume and the mean transit time of this pool.

Without knowing the pool volume the mean transit time can be expressed in terms of cc's per minute per cc of pool volume. Thus the number of cc's of blood flow per minute per cc of pool volume becomes 60/mean circulation time in seconds. The clinical usefulness of this mode of expression of brain blood flow remains to be seen.

SUMMARY

A technique is described in which the mean circulation (transit) time of each hemisphere is determined by means of an intravenous radioisotope technique. A sharp bolus of a rapidly excreted I^{131} labeled compound is released from an antecubital vein. The time of entrance into the brain blood pool of the densest portion of this bolus is determined by plotting the first derivative of the amount of isotope seen in the brain by a paired external collimation-detection system. The time of exit of the densest portion of the bolus is also similarly determined. The interval between the entrance and exit represents, we believe, the mean cerebral transit time.

In 15 normal males transit times were obtained between 6.5 and 10 seconds.

The test is virtually painless, repeatable, and exposes the patient to minimal radiation.

ACKNOWLEDGEMENTS

The author is indebted to Drs. Benedict Cassen, Paul Crandall, and William Blahd and to Mr. Stephen Cross for their many suggestions.

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The Determination of Cerebral Circulation Time

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Since the advent of cerebral arteriography, considerable interest has been expressed in the types of circulation found in the presence of hematoma, tumor and vascular occlusion. In certain of these intracranial processes, there is a very fast circulation. In others, there may be considerable slowing. (5) In some instances, there has been virtual absence of intracranial circulation attributed to the presence of an elevated intracranial pressure. (4) Many of these subtle changes in circulation have been noted only in a discontinuous fashion by angiography.

For the past year we have been interested in devising a direct method of observing transients in the cerebral arteriovenous circulation, because tests used in the past require multiple sampling of either the internal carotid or jugular vessels. (3) Other estimations based on the observation of flow in arterial seriograms give a momentary, animated evaluation of cerebral blood flow and at best can be used only as a check of more precise measurements. However, we have devised a test which is not limited by the length of observations, multiple intermittent samplings or insensitivities of the apparatus.

METHOD

At the time of cerebral angiography (Fig. 1) a No. 18 needle is placed in the common carotid artery. After injection of 50 per cent Hypaque, a seriograph is obtained from which measurements of the arteriovenous transit time can be made. Thereupon the patient is prepared for the radioactive technique by placement of one DS8-1 (Nuclear Chicago Corp.) probe over the internal carotid artery and another over the confluence of the sinuses of the brain. These probes have severe collimation and a small crystal (5 mm x 5 mm). By measurement, sharp resolution of point sources as close as 0.5 cm. is possible with this type of detector. In (Fig. 2) one may note the major arterial input, the capil-

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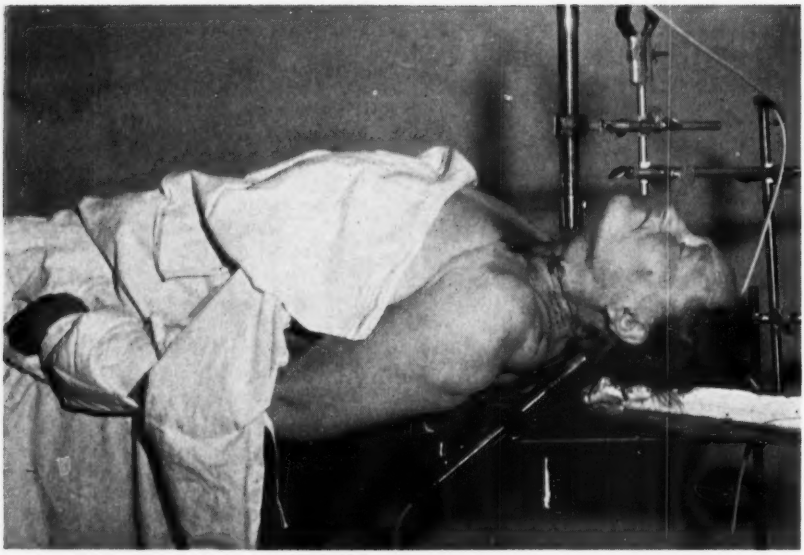

Fig. 1. Physical arrangement of probes. Note needle in situ in the carotid artery.

laries and the confluence of the major venous output. After the injection of either 100 Microcuries of RISA (I^{131}) or Neohydrin, (Hg. 203), we are able to obtain counting rates up to 100,000 counts per minute at the site of the carotid injection. The activity is first localized to the arterial detector and after a period of time

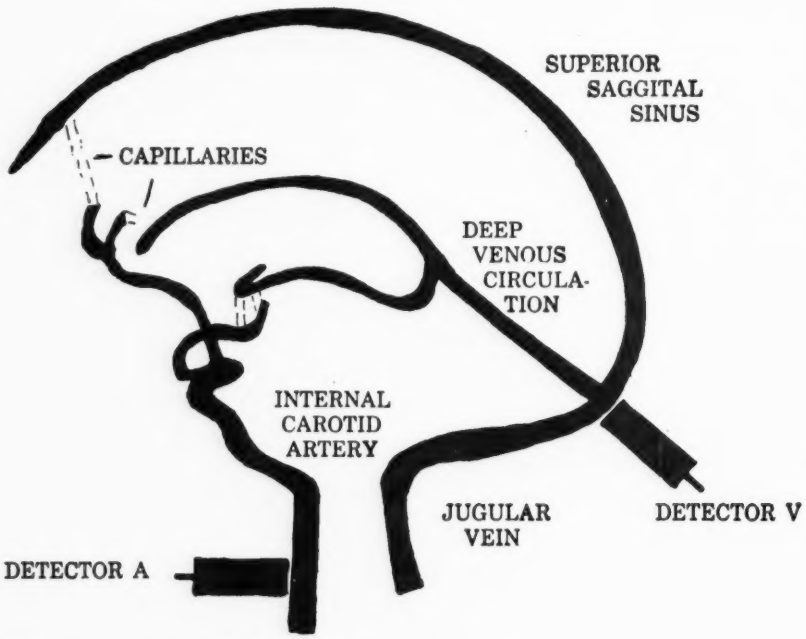

Fig. 2. Schematic of the major arterial and venous channels.

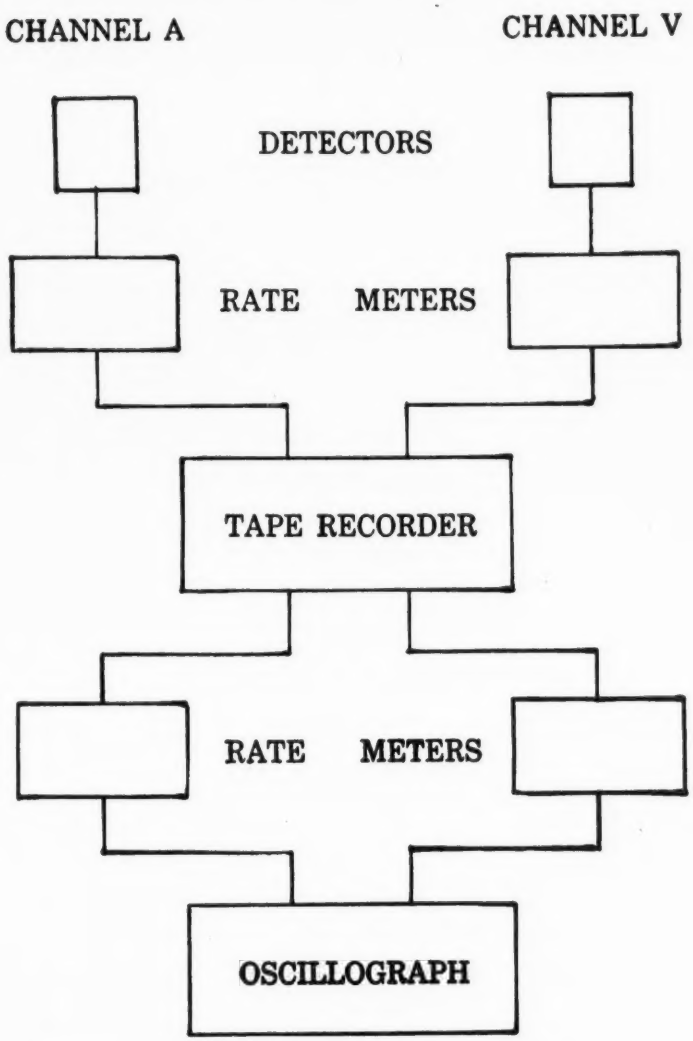

Fig. 3. Block diagram of the dual channel detecting and recording system.

to the venous detector where the counting rates will vary according to the conditions found in the cerebral circulation.

The schematic diagram (Fig. 3) indicates the sequence in the recording of the data. The rate meters have been modified so that the pulses are not observed on the meter. This obviates the long delay and lag time and the build up of the reading on the meter. The pulses are fed directly to a dual channel tape recorder. The same rate meters are used later to receive the data from the recorder. The tape recorder may be varied in recording or playing speed so that

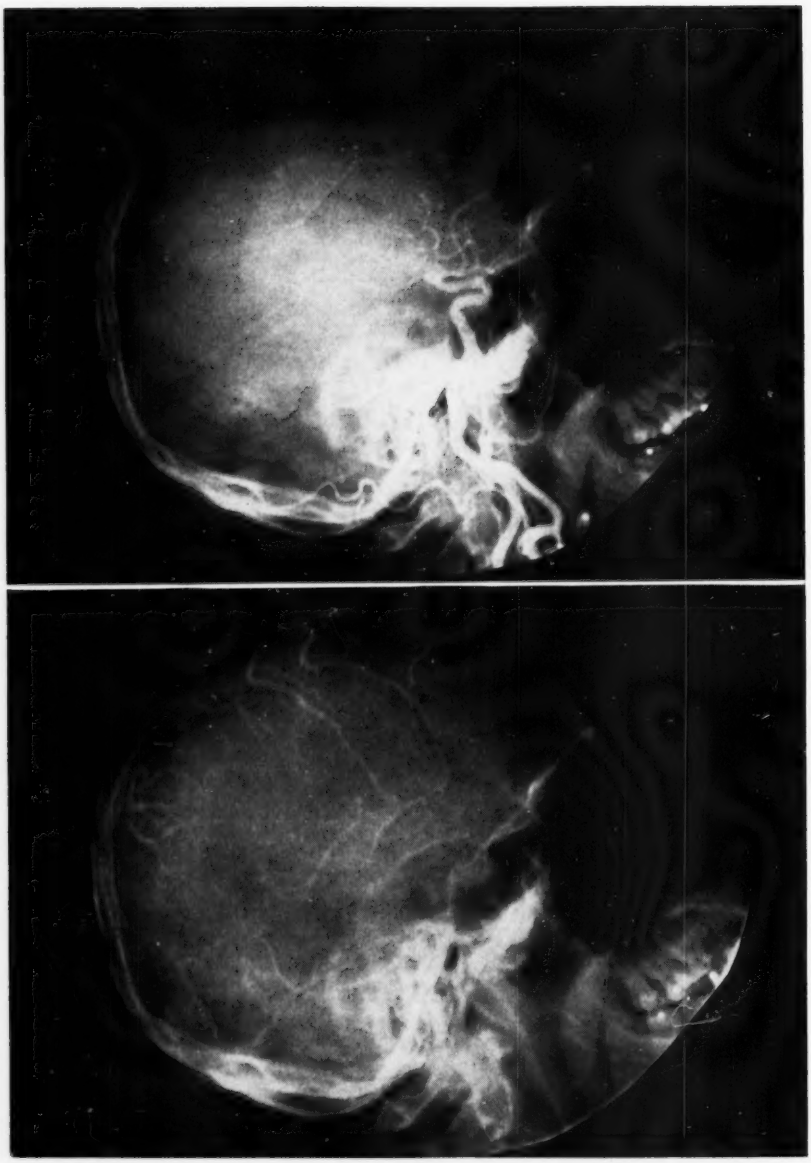

Fig. 4. (Top) (A) A typical angiogram at the start of arterial filling.
(Bottom) (B) The same patient. There is now good venous filling.

the data may be compressed or expanded at will. After processing the tape pulses through the rate meters, the final recording is made on an oscillograph.

RESULTS

Eighteen patients were observed who had a variety of cerebral vascular occlusions, probably as a result of cerebral arteriosclerosis. The circulation times varied between 10.5-14 seconds. Another four patients harbored malignant gliomata and these circulation times varied between 5.2-8 seconds. Three patients were observed who were later proven to have subdural hematoma and had prior to surgery prolonged slowing of the circulation times from 12.5-20 seconds. Five patients were considered to have normal circulation times 6-8.5 seconds.

A typical arteriogram examination is presented (Fig. 4). The first picture corresponds to 0 seconds. The second picture shows the first good venous filling 7½ to 8 seconds later. The tracing obtained by the radioactive technique is shown (Fig. 5). The time marker interval is 0.3 of one second. The lapse between the arterial maximum and venous maximum was measured at 7.2 seconds and was considered to be normal.

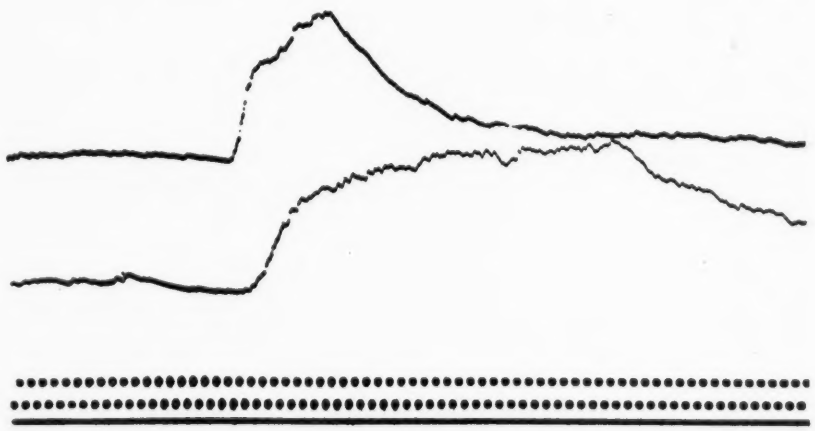

Fig. 5. The radioactive tracing. Artery above. Vein below.

The second patient to be presented had a good beginning arterial filling at 0 time (Fig. 6) and at the end of 13 seconds had poor venous filling. This patient harbored a right temporal lobe hematoma. The radioactive tracing (Fig. 7) revealed a good arterial level, but a very slowly rising venous level which persisted for a relatively long time. These two cases are good examples of the correlation found between the angiogram and the radioactive circulation time. In each of the patients studied by the combined methods, there has been good correlation between what has been observed by the intermittent animated arterial seriogram and the more dynamic observations obtained with the radioactive technique.

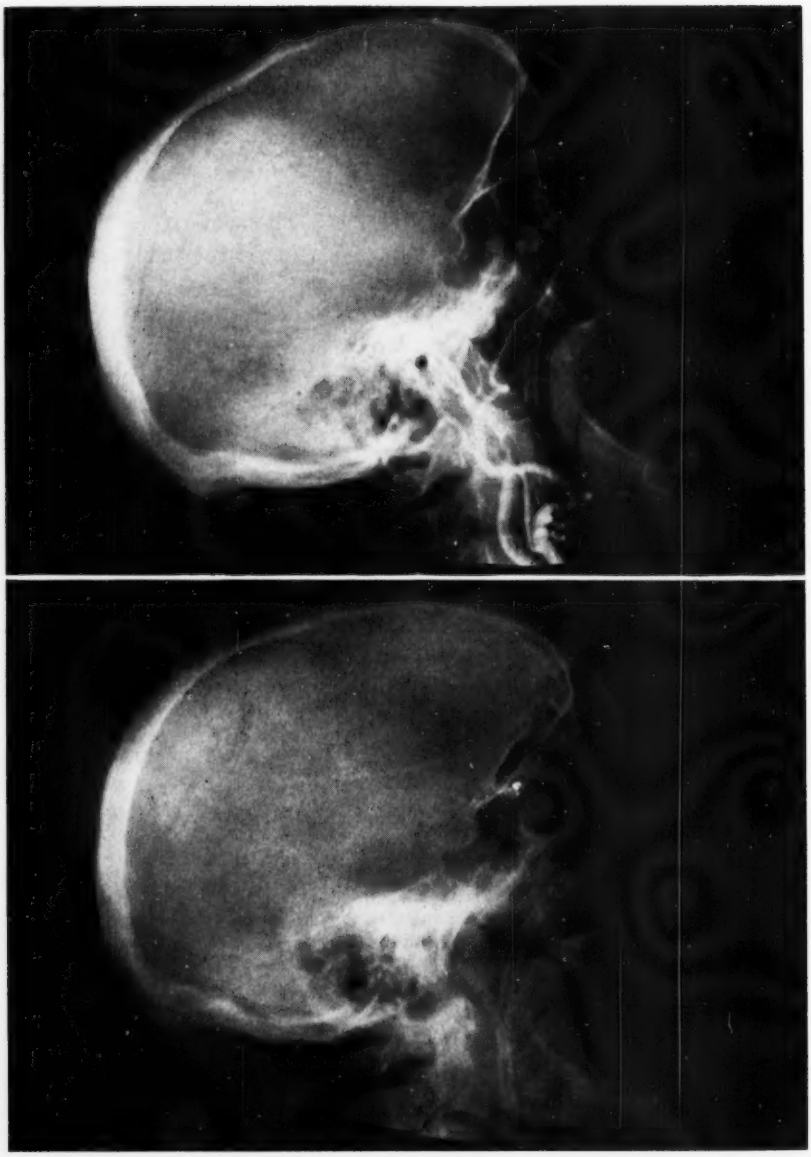

Fig. 6 (Top) (A) Angiogram at start of arterial filling.
(Bottom) (B) Poor venous filling after prolonged period.

DISCUSSION

The radioactive technique for the measurement of arterial venous transit times has several outstanding advantages. The material used in the measurement is usually RISA (I^{131}). Neohydrin (Hg. 203) has been used in several cases because it has the distinction of having but a single gamma energy which simplifies shielding and detecting problems. Most of the Neohydrin is secreted in the urine within 6-8 hours following injection. However, some of the material may be retained in the kidney tubules for prolonged periods of time. (2) We are not aware at this time of the effects of retained radioactive Neohydrin within the kidney tubules. To minimize the effect of possible tubule retention some would recommend premedication with a dose of non-radioactive Neohydrin. (1) Radioactive Neohydrin should not be used in repeated doses until this problem has been resolved.

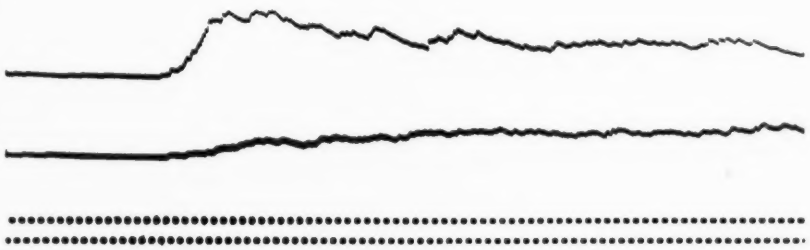

Fig. 7. The same patient but now a radioactive measurement. Artery over vein. Note poor, slow venous fill.

The detecting system has a resolving time in the order of 100 Micro seconds and therefore there is little or no delay between the observing and the recording of the data. Subtle variations in the counting rate are easily observable. The recording of the data on tape permits unlimited recording time and indefinite storage of the record. The tape recording lends itself to compression or expansion of the data thereby permitting enhancement of display in the record.

Ultimate limitation of the method lies in the design of the probe, including its collimation, and angulation in the placement of the probe. There is a small amount of the contribution to the venous tracing by arterial activity and likewise venous activity which contributes to the arterial tracing. This, of course, can only be brought to a irreducible minimum because of the interposition of skin, bone, and meninges. With more severe collimation and accurate placement of the probe the effect of arterial and venous contamination can be limited.

We have not been able to make an accurate statement regarding our ability to measure volume of flow. It is readily recognized that the data does not lend itself to simple analysis as do the cardiac output measurements.

SUMMARY

A method is described which permits the semiclosed measurement of arterial venous circulation times. These measurements can be correlated with those obtained by serial arteriography.

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A Simplified Method for Immuno-Assay of Human Serum Insulin[1]

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INTRODUCTION

The insulin immuno-assay procedure developed by Yalow and Berson(1) makes possible the detection of physiologic levels of serum insulin(1,2,3) and is thought to be specific for insulin. Insulin antibody is incubated with serum insulin and the percentage of the insulin which is antibody-bound varies inversely with the insulin concentration. When subjected to paper strip chromatography, the free or unbound insulin remains at the origin and the antibody-bound fraction moves with the serum proteins. Using a tracer quantity of radioactive insulin, the amount of insulin in each fraction is determined from actagraph tracings of the chromatography strips. As the quantity of insulin increases, a lesser fraction is antibody-bound and a greater fraction remains at the origin.

To obtain the desired sensitivity, Yalow and Berson found it was necessary to prepare I^{131} labelled insulin of high specific activity, 75 to 300 mc/mg. At this level radiation damage to the insulin is appreciable and careful purification to remove breakdown products is necessary. Since commercial insulin is only available at specific activities of approximately 5 mc/mg, it is unsatisfactory for this procedure. The production and purification of high specific activity insulin I^{131} somewhat limits the application of this procedure.

Since the paper strip chromatography procedure utilizes only 0.1 or 0.2 ml of serum, it was reasoned that by increasing the quantity of material studied, commercially available tracer insulin of lower specific activity could be used and the same counting accuracy maintained. This was accomplished by the separation of free and antibody-bound insulin with an anion exchange resin. Free insulin combines with the resin and the insulin-antibody complex does not. Thus, the two fractions can be separated in any volume of material and the percentage of each calculated.

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[1]From the Radioisotope Service, Wood Veterans Administration Center and Departments of Medicine and Physiology, Marquette University School of Medicine, Milwaukee, Wisconsin.

MATERIALS

Anti-insulin antisera: The anti-insulin antibody was produced by injecting guinea pigs with either human or commercial beef-pork insulin. The human insulin was extracted from pancreas obtained at autopsy according to the procedure of Jephcott(4) and was assayed for insulin activity by the mouse convulsion technique(5). Four guinea pigs were injected with human and four with beef-pork insulin. One unit was injected subcutaneously twice weekly. After eight weeks or longer, the injections were discontinued for two to three weeks and blood for serum was then drawn by cardiac puncture from fasting animals. Approximately 10 ml was drawn every three months.

The guinea pig serum was diluted so that 0.1 ml added to 20 microunits (μU) of insulin standard would bind 65 to 75 per cent. Added to a 100 μU standard, it would bind 25 to 35 per cent.

Tracer insulin: Insulin I^{131} was obtained from Abbott Laboratories[1] with a specific activity of approximately 5 mc/mg. One-tenth or two-tenths millimicrograms (mμg) was added per ml of sample to be assayed. Studies in our laboratory indicated that this insulin contained about 16 U/mg. Subsequent information from Abbott Laboratories confirmed this value. The added tracer insulin would therefore equal 1.6 or 3.2 μU/ml.

Ion exchange resin: Several anion exchange resins were studied for their ability to bind insulin. These included Dowex 1 and 2 and Amberlite 400 and 410 and the chromatographic grade Amberlite CG-400. In the chloride form, they would completely extract free insulin from saline or albumen, however, they would only extract 30 to 60 per cent of unbound insulin added to serum. Similar results were reported by Mitchell(6). In the hydroxide form, the resin would completely remove free insulin from serum. Because of its anhydrous property, the chromatographic grade Amberlite CG-400 was found most satisfactory.

The Amberlite CG-400, obtained commercially in the chloride form,[2] was partially cycled to the hydroxide by mixing at room temperature for 2 hours in 8 volumes of 2N sodium hydroxide. The resin was then filtered in a Buchner funnel and washed with distilled water until the pH of the filtrate was below 8. It was then air dried and stored in an amber colored bottle.

Insulin standards: Known concentrations of human or beef-pork insulin were diluted in 6 per cent albumen to give from 3 to 405 μU/ml. Six concentrations were usually used.

Human serum insulin studies: Serum insulin levels were determined during a standard glucose tolerance test of healthy normals and adult, maturity onset, diabetic patients who had been controlled by diet alone. Blood samples were placed immediately in a refrigerator although bloods allowed to clot at room temperature did not show any significant loss of insulin.

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[1]Abbott Laboratories, Oak Ridge, Tennessee.

[2]Rohm and Haas Company, Philadelphia 5, Pa.

PROCEDURE

One-half ml of the diluted antisera was added to 5 ml of labelled serum. The mixture was then incubated for 24 hours at 2-4° C. Two ml of the incubated mixture was then added in duplicate to test tubes containing 200 mg of the previously prepared Amberlite CG-400 anion exchange resin. The total activity was counted in a well counter equipped with a single channel spectrometer. The sample was then placed in a constant-temperature water bath, at 25° C and shaken at a speed of about 180 cycles per minute. Shaking continued for one hour. After centrifugation, one ml of the supernatant was removed, diluted to 2 ml, and the activity counted. Two times this activity represented the antibody-bound insulin in the 2 ml aliquot of the serum-antiserum mixture. This value divided by the total radioactivity of the 2 ml aliquot obtained prior to mixing with the resin gave the antibody-found fraction.

In order to quantitate the amount of insulin present in the serum, several known concentrations of human or beef-pork insulin were assayed simultaneously. These "standards" were diluted in 6 per cent albumen to concentrations ranging from 3 to 405 μU/ml. The concentration of insulin present in the serum is then calculated as that quantity of a standard concentration of insulin which would give the same per cent binding as was obtained with the serum.

DISCUSSION

On occasion, guinea pig serum obtained for insulin antibodies a fews days after the last insulin injection was unsatisfactory for the assay. This material did not yield a progressively increasing per cent antibody bound fraction with decreasing insulin concentrations below 20 μU/ml. If insulin was discontinued for longer periods this undesirable feature was not observed. Therefore, cardiac puncture was not performed until at least two weeks after insulin had been discontinued.

The insulin antibody reaction is a mass action type which is both time and temperature dependent. Twenty-four hour incubation in the refrigerator was chosen since the binding is adequate and small variation in time has little effect. The per cent antibody bound in relation to incubation time at 2-4° C is illustrated in Fig. 1, which shows two separate unrelated studies using different concentrations of insulin. In either case, the antibody-bound fraction after 24 hour incubation, was about 75 percent of the binding at 96 hours. After one hour incubation at room temperature, the binding was found to be comparable to that after 24 hours at 2-4° C. However, the incubation timing was quite critical and results were not as reproducible. Longer incubation at the higher temperature was precluded by the increase in insulin destruction. At 2-4° C, the 24-hour incubation can vary by one hour and not appreciably alter the results. Since one hour was usually required in preparation of samples, the 24-hour incubation in the refrigerator was routinely adopted. As standards are run with each study it was only necessary that incubation time was equal for all samples.

Adequate mixing of the serum and anion exchange resin was accomplished in a constant temperature bath with an improvised shaker, Fig. 2. A plastic test

tube holder moves back and forth on the tank top. The angle of the tubes and the speed of the shaker can both be varied with ease.

As shown in Table 1, the quantity of resin used can be varied over a wide range without appreciably altering the result. At the two insulin concentrations

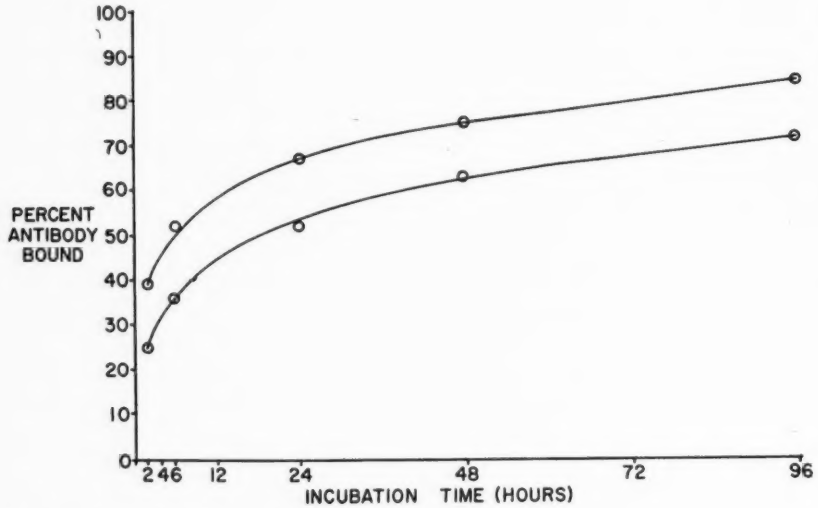

Fig. 1. Effect of incubation time at 2 - 4°C on antibody binding

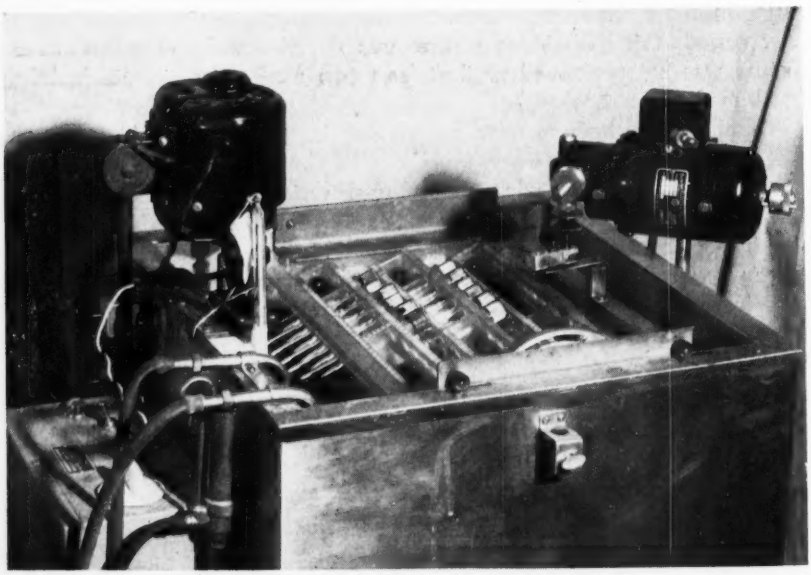

Fig. 2. Constant temperature shaker with tubes in place

shown the resin-bound or free insulin fraction appears independent of the quantity of resin.

The binding of the free-insulin radioactivity to resin was most rapid during the first few minutes of mixing. The results obtained from four different insulin concentrations are shown in Fig. 3. At the higher insulin concentration, there was little antibody binding and the binding of free insulin to the resin was nearly complete in 15 minutes, upper curves. At the lower insulin concentration, lower curves, more of the insulin was antibody bound leaving less to combine with the resin. In this situation, there was a significant increase in resin binding with time. Since the binding equilibrium is reversible the removal of free insulin by the resin would accelerate dissociation of the insulin-antibody complex. To reduce this effect and maintain adequate mixing, a mixing time of exactly one hour was chosen.

A comparison of the per cent antibody-bound insulin determined by paper strip chromatography and anion exchange resin is shown in Table 2. Insulin I^{131}, 10 mμg per ml, was added to the serum of 5 diabetic patients who had been receiving insulin. The chromatography was done using barbital buffer and the

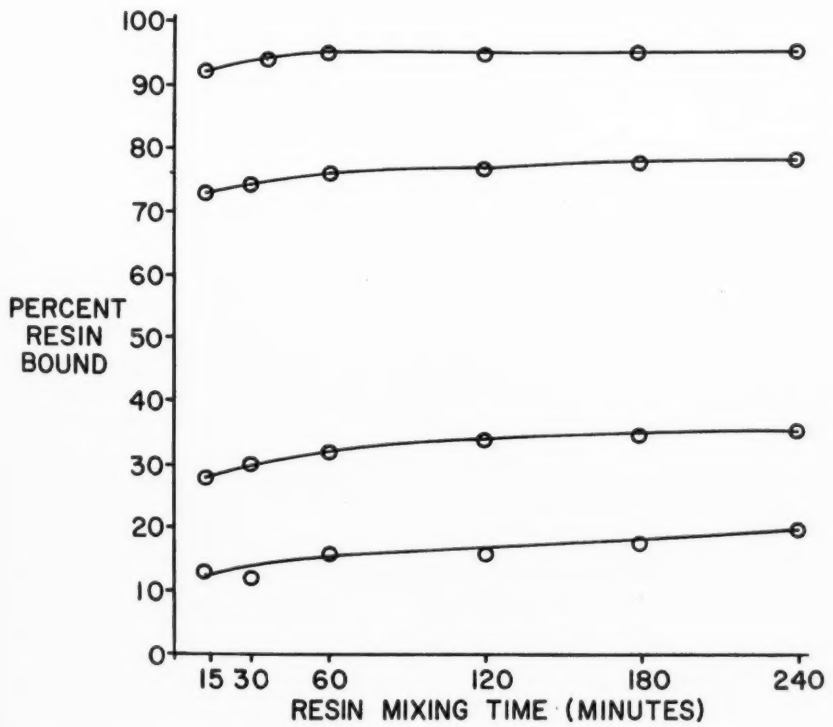

Fig. 3. Effect of resin - serum mixing times upon the resin binding of iodoinsulin. Illustrated are 4 levels of antibody binding - differences from 100 equals percent antibody bound

serum front allowed to travel 12 cm. The strips were then dried, cut midway between origin and front and the activity in each fraction counted in a well counter. In general, the results obtained by the two procedures are comparable.

It should be pointed out that heparinized plasma was unsatisfactory. As was previously noted with thyroxine, heparin inhibits the adsorption of insulin by the resin. To avoid the possibility of interference from other anti-coagulants, only serum was used.

The standards used for the assay were diluted from commercial beef-pork insulin. The assay of human insulin was based upon a comparison of the ability

TABLE 1.

RELATIONSHIP OF QUANTITY OF RESIN USED TO THE PER CENT OF INSULIN I^{131} RESIN-BOUND

Quantity of Resin	*Per Cent of Insulin I^{131} Resin-Bound*	
	Insulin Concentration μU/ml	
mg	*405*	*270*
100	90.4	68.8
200	92.2	75.1
300	91.5	70.9
400	89.2	75.2
500	91.2	76.3

TABLE 2.

INSULIN BINDING BY DIABETIC SERUM COMPARISON OF PAPER STRIP CHROMATOGRAPHY AND ANION EXCHANGE RESIN

Percent of Insulin Antibody-Bound	
Paper Chromatography	*Anion Exchange Resin*
59.7	52.2
46.5	43.2
80.6	85.8
84	87.1
82	87.5

of insulin antibody to bind human insulin and the ability of the same antibody to bind commercial beef-pork insulin. This method was valid only if there was no species specificity of the guinea pig antibody. Since some guinea pigs were injected with human insulin and some with beef-pork insulin, it was possible to compare the binding of both human and beef-pork insulin by anti-human or anti-beef-pork insulin antibody. Table 3 demonstrates that the human and beef-pork insulin assayed by either anti-human or anti-beef-pork anti-sera showed no species specificity. The two types of insulin were diluted to give equal binding with beef-pork antibody as shown at three concentrations. The same dilutions also gave equal binding using human insulin antibody. It was therefore concluded that binding values obtained for beef-pork insulin, using guinea pig anti-beef-pork insulin antisera, could be transposed to human insulin equivalents. Similar results have been reported by Grodsky and Forsham(7) and Yalow and Berson(8).

To compare the immunoassay to another method of insulin assay, the human insulin was assayed against commercial beef-pork insulin by both the immunoassay and mouse convulsion technique of Scott(5). The activity of the human insulin as determined by each assay method is shown in Table 4. By

TABLE 3.

NON-SPECIFICITY OF GUINEA PIG ANTISERA

Insulin Antibody	*Insulin Concentration μU/cc*	*Percent Antibody Bound*	
		Beef-Pork Insulin	*Human Insulin*
Beef-Pork	405	43	42
	135	77	75
	27	87	87
Human	405	29	32
	135	49	52
	27	82	82

TABLE 4.

ASSAY OF HUMAN INSULIN

Type of Assay	*Insulin Concentration Units/cc*
Mouse Convulsion	0.32
Immuno-assay	0.25

immuno-assay, the insulin was calculated as 0.25 U/ml. By mouse convulsion assay, it was calculated as 0.32 U/ml. Since only 40 mice were injected with each type of insulin, the convulsion assay cannot be assumed highly accurate. Nevertheless, the results obtained by the two methods are comparable.

The standard curve for serial dilutions of commercial beef-pork insulin in albumen is shown in Fig. 4. Insulin concentration in μU/ml is shown on the base line. The upper curve is the per cent of insulin which is antibody-bound and the lower curve is the bound-to-free ratio. Fasting levels of serum insulin are near 20 to 25 μU/ml which has 70 to 80 per cent bound. The insulin level rises to 100-200 μU following glucose or the per cent bound insulin falls to near 20 per cent. Physiologic levels therefore fall on the most sensitive part of the curve.

The reproducibility of the standard curve is shown in Fig. 5. The range of values obtained for six consecutive studies done over a four-week period are shown here. The same guinea pig anti-sera and the same insulin was used. The insulin I^{131} was from three different shipments from Abbott Laboratory. Although the values are fairly constant, it is considered advisable to run a separate set of standards with each study.

The ability to recover insulin added to serum and the reproducibility of the procedure is shown in Table 5. Known amounts of insulin were added to human serum which was refrozen between successive studies. Each run represents the average of duplicate determinations. The assays were determined during a

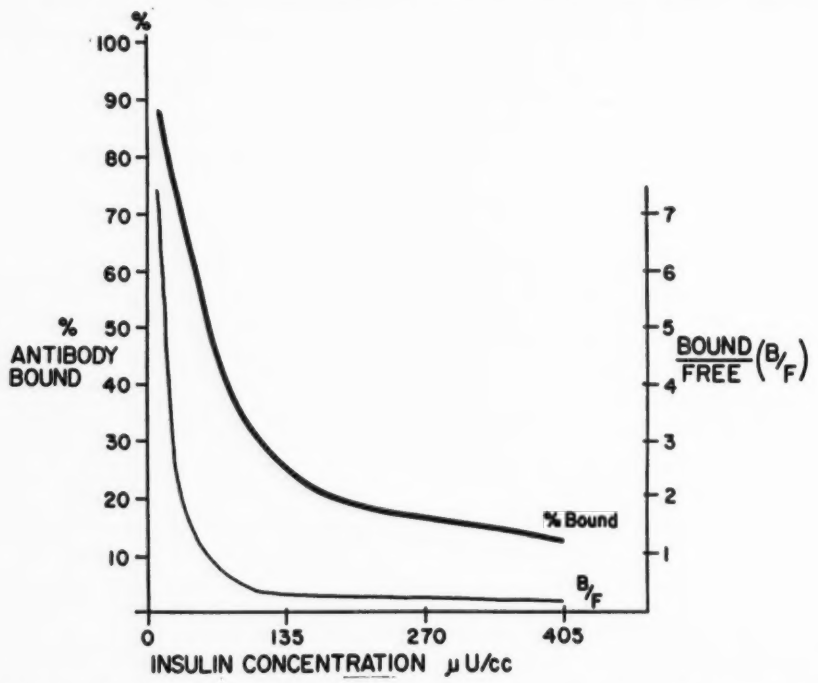

Fig. 4. Standard dilution curve showing effect of insulin concentration on the percent antibody bound and bound-to-free ratio

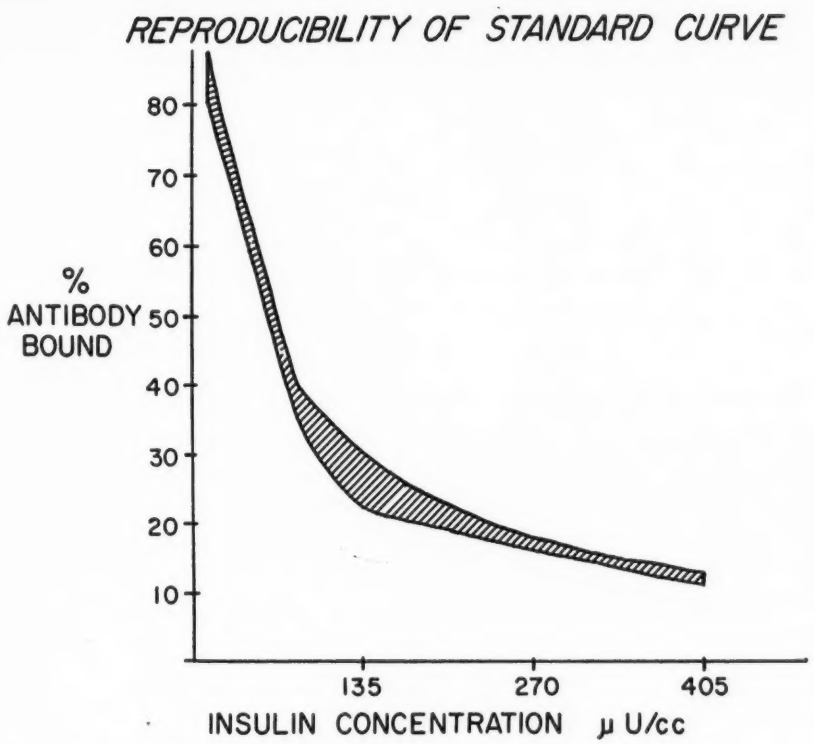

Fig. 5. Limits of variation of 6 standard dilution curves run over a 4 week period

TABLE 5.

RECOVERY OF INSULIN ADDED TO HUMAN SERUM—3 SEPARATE ASSAYS

Added Insulin μU/ml	*Recovery μU/ml*		
	1	*2*	*3*
27	32	30	35
81	110	100	103
135	151	146	151
270	281	286	284

seven day period using a single guinea pig antiserum. Although the values are about 10 per cent higher than expected, the successive studies compare well.

To illustrate the practicality of the procedure serum insulin levels obtained during glucose tolerance tests are shown for the average of ten normals and four-

TABLE 6.

SERUM INSULIN-RESPONSE TO ORAL GLUCOSE

Sample	*Serum Insulin Concentration μU/cc*	
	Normal-Average	*Diabetic-Average*
Fasting	11	22
15 Min.	51	50
30 Min.	68	75
1 hr.	78	115
1½ hr.	72	121
2 hr.	53	115
3 hr.	26	81

teen adult maturity onset diabetic patients who had been controlled by diet only, Table 6. These values, although lower, are similar to those reported by Yalow and Berson(2). Fasting levels are the same in each group, the rise is less rapid in the diabetics and the return to normal fasting levels is delayed.

SUMMARY

A method of immunoassay of insulin and its practical application in detecting normal levels of serum insulin has been presented. Guinea pig serum containing the insulin antibody is incubated with serum or known concentrations of insulin in albumen and tracer amounts of insulin I^{131}. Following incubation, the free or non-antibody-bound insulin is removed by an anion exchange resin. The fraction of insulin antibody-bound is calculated and compared to the binding of known amounts of insulin. The method is felt to be accurate, reproducible and applicable to the smaller radioisotope laboratory.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Mrs. Ronald T. Aushwitz and Mr. Robert A. Stiglitz for technical assistance in this study.

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JOURNAL OF NUCLEAR MEDICINE 3:417-421, 1962

A Chromatographic Method Utilizing Sephadex for the Separation of Free Iodide, Protein-Bound and Unbound Triiodothyronine in Sera

A) Clinical Correlations With the Hamolsky T-3-RBC Uptake Method. (108 Cases)

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INTRODUCTION

In 1957 Hamolsky, Stein, and Freedberg (1) described a practical *in vitro* method for the study of thyroid function by measuring the human erythrocyte uptake of I-131 labeled triiodothyronine (T-3) (2,3). This study has proved to be of real value, (4) but the technique is exacting, involves lengthy multiple washings of red blood cells and does not permit correction for the free iodide found in the reagent. (5,6). The mechanism of the differential uptake by patients with thyroid disease (high in hyperthyroidism and low in hypothyroidism) appears to involve the plasma protein binding of thyroid hormone (7,8). Hamolsky, et al (1,2,3,) showed that hyperthyroid plasma mixed with euthyroid red blood cells resulted in high uptake of T-3 by the cells and that euthyroid plasma mixed with hyperthyroid red blood cells resulted in a normal uptake of T-3 by the cells. A possible explanation was that if the binding sites for thyroid hormone were saturated, the T-3 would be free to enter the cells in abnormally large amounts. If such were the mechanism it would seem possible to make the same measurements by a direct study of the protein binding of T-3 added to human plasma or sera. Such an approach has been used by several investigators using ion exchange resins to remove the T-3 which was not protein bound (9,10). The present paper describes a new technique for measuring the protein binding of T-3 by sera (11). This method is less exacting, and much easier to perform than the T-3 RBC uptake technique. The results obtained (Fig. 1) are equally reliable.

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METHODS

Materials. A preparation containing 15 μg of pharmaceutical grade I-131 labelled triiodothyronine per ml was the "stock" solution used. The specific activity of this solution was 34.3 μc/μg (514 μc per ml). Before carrying out tests, the stock solution was diluted; (to 0.1 ml of solution 50 ml of M/15 phosphate buffer was added). The chromatographic adsorbent used was commercial medium grade "Sephadex G-25" (Pharmacia Corp.). Two grams of this "Sephadex" were slurried in phosphate buffer solution and added to a glass chromatographic column 1 cm diameter. This column was tapped with a rubber hammer to obtain homogeneous sedimentation. The columns were provided with glass jackets through which water at 37° C was pumped. (This temperature control is valuable only when noticeable changes in temperature may occur in the laboratory).

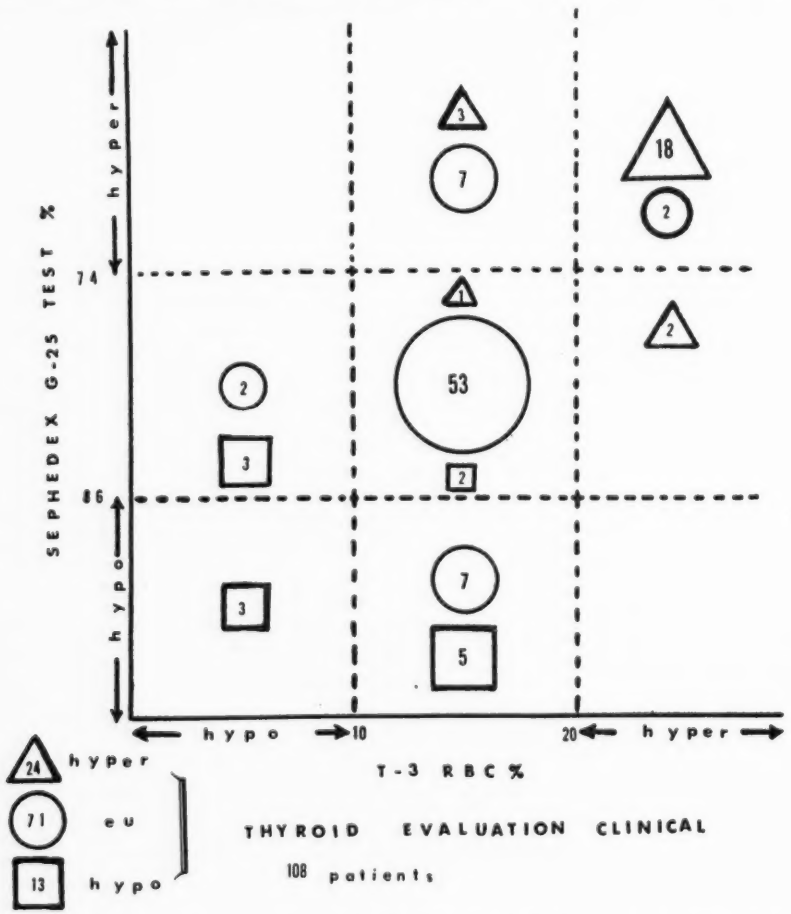

Figure 1. Relationships between "Hamolsky T-3 RBC % uptake" test and "Sephadex G-25 % uptake" test of 108 clinically evaluated patients (not under treatment)

PROCEDURE

A volume of 0.1 ml of diluted I-131-T-3 solution was added to 3 cc of human serum in a test tube. The tube was placed in a water bath at 37° C for 15 minutes (protein binding is so rapid that only a few minutes are necessary (11)). One cc of this treated serum was removed and assayed in a scintillation well counter while a second cc of the serum was placed on the column. Two 1 cc portions of buffer solution were added to the top of the chromatographic column, allowing the fluid level above the "Sephadex" to move down to the surface of the Sephadex column in each case. Buffer solution was then added to the column and 1 ml eluate fractions were collected until 11 such fractions were obtained. These fractions were then individually assayed in a scintillation well counter.

Fraction #1	none or little activity
Fractions #2-4	protein bound I-131
Fractions #5-6	little activity
Fractions #7-11	free I-131

Calculations:

a. Deduct background from all counts.

b. Sum up counts in those fractions containing protein-bound I-131.

c. Sum up counts in those fractions containing free I-131.

d. Subtract free I-131 counts from net counts in serum to obtain net counts protein-bound I-131 in serum.

e. $$\frac{\text{Net counts protein-bound I-131 fractions}}{\text{Net counts protein-bound I-131 in serum}} \times 100$$

f. Approximate values:

Normal	74-86%
Hyperthyroid	below 74%
Hypothyroid	above 86%

In preliminary experiments it was ascertained that this "column" could be used for the separation of: a) I-131-T-3 in phosphate buffer, I-131-NaI and I-131 labeled human serum albumin; b) I-131-NaI mixed with sera, and c) I-131-T-3 and sera. It was shown that T-3 in buffer solution when added to a Sephadex column would remain on the column. I-131 as NaI could be eluted from the column with buffer and would come off the column as a separate peak usually in the sixth to eighth fractions. Proteins came off the column in the second to fourth fractions. When T-3 was added to the column in a buffer solution, it would remain on the column but could be removed by addition of serum. Over 90 per cent of the "T-3" could be removed by serum under these conditions. These results suggested that it would be possible to measure the per cent of "T-3" bound by serum proteins by measuring the first peak of radioactivity removed from the column by elution with buffer and comparing it to the total activity added to the serum. "T-3" not bound by protein would remain on the column. Any free iodide

present in the "T-3" would come off as a separate peak in the sixth to eighth fractions and could be measured for correction of the amount of radioactivity used as "T-3".

RESULTS

The results obtained in this study of 108 evaluated patients (not under treatment) by using this method, are shown in Figure 1. The "T-3 RBC per cent uptake" was compared with the serum protein binding as measured by "Sephadex". The normal range used for "T-3" was 10 to 20 per cent and the normal range using "Sephadex" was 74 to 86 per cent. It can be seen that most of the values obtained by the "Sephadex" technique correlated well with those obtained by the "T-3-RBC" uptake technique. There are several hyperthyroids who had normal "Sephadex" values and several normal patients with hyperthyroid "Sephadex" values, but this discrepancy applied to the "RBC-T-3" determination as well. With euthyroids, 67 gave the expected result while 4 gave unexpected values using "Hamolsky's" method; while "Sephadex" gave to 55 the expected result and for 16 unexpected values. There seemed to be almost as many errors or unexplained results with one test as with the other.

DISCUSSION

The described techniques appeared to us to be about as good as the red cell uptake technique in the determination of thyroid function. However, the former seems to be much simpler and more convenient to do. The presence of free iodide in the reagent can be easily corrected. The red cell washing which is a time-consuming and tedious procedure, is eliminated. There is also no difficulty with hemolysis. The entire procedure occupies less than an hour and can easily be handled by a laboratory technician. No correction is necessary for hematocrit. The fact that there is such good correlation between these two techniques is further evidence that we are measuring protein binding indirectly when we do the red cell uptake studies.

The mechanism of the Sephadex G-25 separation is not well understood; (Sephadex is known to bind compounds with aromatic rings). The Sephadex removes the unbound "T-3" but apparently cannot compete with the stronger "T-3" protein binding of the plasma. Experiences with this technique indicate it to be very useful in the study of thyroid problems and may also be of value in obtaining a better understanding of protein binding of thyroid hormones.

SUMMARY

a) A new method was presented for the *in vitro* evaluation of thyroid function. This method consists of the chromatographic separation of protein bound and unbound T-3 and free-iodide from sera by a Sephadex G-25 column.

b) Comparative results of the "RBC-T-3" and "Sephadex" uptakes of 108 clinically evaluated patients are presented.

c) This method is less exacting, easier and faster than the "RBC-T-3" and just as significant.

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JOURNAL OF NUCLEAR MEDICINE 3:423-435, 1962

The Anemia of Leukemia[1]

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In 1906 Hirschfeld (1) suggested that the anemia of leukemia resulted from replacement of red bone marrow by leukemic tissue and an increased destruction of erythrocytes. The concept of marrow infiltration with decreased hematopoiesis has been widely accepted, but recent work has shown that it is not the only mechanism involved. In fact morphologic evidence of increased erythropoiesis has been found in chronic granulocytic leukemia (2-4). Radioisotopic studies in all types of leukemia have shown both increased and decreased formation (5-12) and normal or increased destruction of erythrocytes (5, 11, 13-19). Bleeding into the gastrointestinal tract, although considered a contributory cause of the anemia, has never been measured.

The present study was undertaken to obtain further information about the mechanism of anemia in leukemia with particular reference to production and destruction of erythrocytes and loss of blood from the gastrointestinal tract.

MATERIAL AND METHODS

A combined radioiron and radiochromium technic was used to investigate the anemia of eight patients with acute leukemia, two with chronic granulocytic and two with chronic lymphocytic leukemia. The plasma iron turnover alone was measured in two additional patients, one with chronic granulocytic, the other with chronic lymphocytic, leukemia. The dual isotopic studies were carried out for 10 to 22 days on all but two patients who were studied for 5 and 9 days. Data were obtained from one patient with acute leukemia before and after remission. Details of each group will be given with the results.

In every patient undergoing the complete investigation, the blood lost in the stool and the Cr^{51} excreted in the urine were quantitated. The study also

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included assessment of in vivo tissue radioactivity in six patients by external scintillation counting. At postmortem examination organ radioactivity was estimated in two of these patients.

The methods and calculations are those described by Owen (20) except that heparin was used as the anticoagulant for in vitro Fe^{59} tagging. Iron incorporation was determined when possible on plateau values and corrected by the average (0.9) total body to peripheral vein hematocrit ratio.

The serum iron was measured by the method of Ramsay (21, 22).

Chronic Lymphatic Leukemia.—No significant abnormality was found in the kinetics of radioactive iron and chromium in two patients with chronic lymphocytic leukemia whose clinical course was satisfactory.

TABLE 1

NORMAL Fe^{59} DATA

Controls	*Hematocrit, per cent of volume*	*Serum iron, μg./100 ml.*	*$t^{1/2}$ (min.)*	*Turnover of plasma iron*	
				Mg./100 ml. of whole blood	*Mg./kg./day*
1	43	100	133	0.44	0.41
2	45	86	96	0.42	0.33
3	45.5	75	82	0.51	0.42
4	47	98	115	0.47	0.41
5	47	101a	78	0.72	0.42
6	45	135	162	0.48	0.46
7	50	155	120	0.67	0.54
8	47	80	80	0.55	0.40
9	45	122	120	0.58	0.42
10	43	100	86	0.66	0.47
Mean	46	105	107	0.55	0.43

RESULTS

The data for the normal subjects are presented in Table 1.

Acute Leukemia.—The group was comprised of four men and four women with ages ranging from 29 to 82 years (Table 2). The investigation lasted from 10 to 22 days except for patient 6 who died on the fifth day. Four patients had lymphoblastic leukemia, two, myeloblastic leukemia, and two were in the acute terminal phase of chronic granulocytic leukemia. Seven were anemic, having 6.5 to 10.4 gm of hemoglobin per 100 ml of blood. The erythrocytes of all except patients 3 and 5 were normochromic; in these two they were hypochromic.

The serum iron value was in the normal range in six patients and higher than normal in two. Patient 3 with a serum iron level of 247 μg per 100 ml had received 27 units of blood in 4 months. Patient 7 with 290 μg of serum iron was jaundiced as the result of acute infectious hepatitis, but she was not excluded because the results of her tests were in accord with those of the rest of the group.

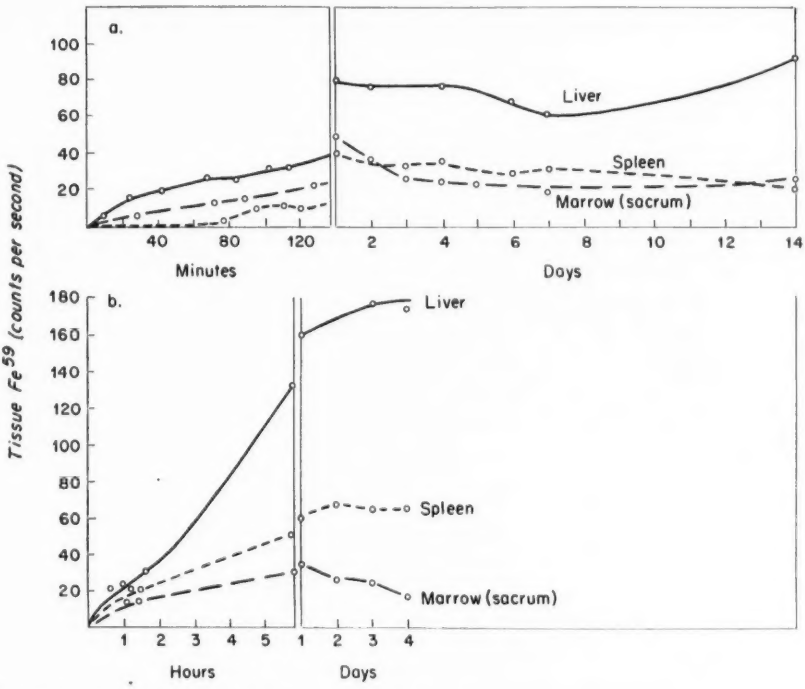

Fig. 1. In vivo organ radioactivity. *a.* Case 3. *b.* Case 6.

The turnover rates of plasma iron per 24 hours ranged as follows: 16 to 97 mg total, 0.19 to 1.41 mg per kilogram of body weight, and 0.42 to 1.14 mg per 100 ml of blood (Table 2).

In all patients the Fe^{59} incorporated in erythrocytes was low, ranging from 10 to 57 per cent of the dose. Patient 3 who had the longest plasma Fe^{59} half clearance time had the highest erythrocytic incorporation, and patient 8 who had the fastest clearance time had the least incorporation.

In seven patients the rate of hemolysis as measured with Cr^{51} was increased; that of patient 5 was at the upper limit of normal. The points on the curve for patient 7, however, were too widely scattered to give a readily interpretable result. In three cases the data were best plotted on semilogarithmic paper instead of on arithmetic paper. This was interpreted as indicating random hemolysis with destruction of cells of all ages.

External scintillation counting for Fe^{59} over liver, spleen, and sacral bone marrow was carried out in three patients with acute leukemia. In patient 5 the bone marrow showed the greatest increase in radioactivity, reaching a maximum in 24 hours and then starting to decline. In patients 3 (Fig. 1*a*) and 6 (Fig. 1*b*), however, the increase in radioactivity was most marked over the liver. Both these patients died during the course of their investigation, and organ counts were performed after death on weighed specimens of tissue. In patient 3 the liver contained 50 per cent of the dose of iron, and the spleen, 4 per cent. In patient 6 the liver contained 70 per cent and the spleen, 10 per cent of the dose.

TABLE 2

CASES OF LEUKEMIA STUDIED

Patient or case	Sex and age, year	Hemoglobin, gm./100 ml.	Hematocrit, per cent*	Serum iron, μg./100 ml.	Plasma Fe^{59}		Turnover of plasma iron			Erythrocyte-labeled Fe^{59} per cent of dose	Cr^{51}, per cent fall/day	Bone marrow, per cent normoblasts	Blood lost daily in stool, ml.
					$t_{\frac{1}{2}}$, min.	Clearance, per cent/hr.	Mg./day	Mg./kg./day	Mg./100 ml. of blood/day				
Acute Leukemia													
1	F 50	9.4	22	112	200	21	17	0.26	0.42	16	4.9†	2.4	17
2	F 82	7.5	32	103	105	40	26	0.46	0.67	56	4.3	17.8	0.7
3	M 48	9.7	29	247	206	20	54	0.51	0.85	57	4.9‡	3.7	1.2
4	F 57												
Before remission		6.5	11	102	206	20	16	0.19	0.44	24	5.0	10.4	2.6
During remission		7.6	24	61	40	104	43	0.56	1.15	97	1.4	20.9	0.7
5	M 57	9.4	33	133	79	53	71	0.81	1.13	55	2.4	10.3	0.6
6	M 29	6.5	16	152	163	25	59	0.78	0.70	10	6.3‡	11.7	5.5
7	F 41	10.4	28	290	198	21	56	0.86	0.89	12	2.7§	‖	3.8
8	M 64	12.2	39	52	25	166	97	1.41	1.14	10	7.8‡	‖	3.8¶

Chronic Granulocytic Leukemia

9	M 69	8.2	26	23	23	180	50	0.87	0.74	48	0.3†	16.8	22
10	M 62	9.7	27	37	21	198	101	1.30	1.25	49	1.9	‖	6¶
11	F 62	11.8	35	95	76	55	29	0.47	0.78			‖	

Chronic Lymphocytic Leukemia

12	M 46	13.7	49	175	95	44	55	0.52	0.93	89	2.5	‖	0.1¶
13	F 64	11.0	35	108	57	73	37	0.68	1.19	90	2.2	2.0 (specimen not representative)	0.4
14	F 63	8.4	26	78	53	78	37	0.45	0.95			‖	

*Hematocrit reading, per cent of volume, corrected × 0.96.
†Corrected for blood lost in the stools.
‡Logarithmic decrease.
§Points on curve were widely scattered.
‖No bone marrow aspiration.
¶Incomplete stool collections.

Patient 4 was investigated before and after remission (Table 2). The initial study was performed 12 days after treatment with an antimetabolic agent (imidazolyl thioguanine) was started. The plasma iron turnover was 0.44 mg per 100 ml of blood per day, and 27 per cent of the dose was incorporated in the erythrocytes. Increased hemolysis was occurring, with a Cr^{54}-disappearance rate of 5 per cent per day. Eight weeks later when the patient was in complete remission, the Fe^{59}-erythrocyte incorporation was 97 per cent of the dose and the Cr^{51}-disappearance rate was within normal limits. Similar results were obtained by Wetherley-Mein and associates (12) who reported the effect of successful treatment of two patients with acute leukemia.

Only patient 1 was losing a significant amount of blood in the stools, an average of 17 ml per day (Table 2). An amount of Cr^{51} equivalent to a loss of 5 ml of blood per day has been found in the stools of apparently normal persons (23). Hemorrhage results in an increased rate of Cr^{51} disappearance from the blood, and a correction was made, therefore, in the observed Cr^{51}-disappearance rate.

Chronic Granulocytic Leukemia.—Two men and one woman, aged 62 to 69 years, were investigated (Table 2). Patient 9 was under observation for 9 days; patient 10 for 10 days. For patient 11 only the plasma iron turnover was determined.

Patient 9 was losing an average of 22 ml of blood daily in his stools. The serum iron measured 23 μg per 100 ml and the erythrocytes showed hypochromasia. The anemia (8.2 gm of hemoglobin), therefore, could be partly explained on the basis of chronic loss of blood. Patient 10 had carcinoma of the urinary bladder with biopsy 3 days before the study began. Subsequent bleeding had required transfusion of 4.5 liters of blood. The Cr^{51}-disappearance curves gave no evidence of hemolysis, although some scattering of the points was noted, presumably owing to the recent blood transfusions. The Fe^{59}-erythrocyte incorporation was low in both cases.

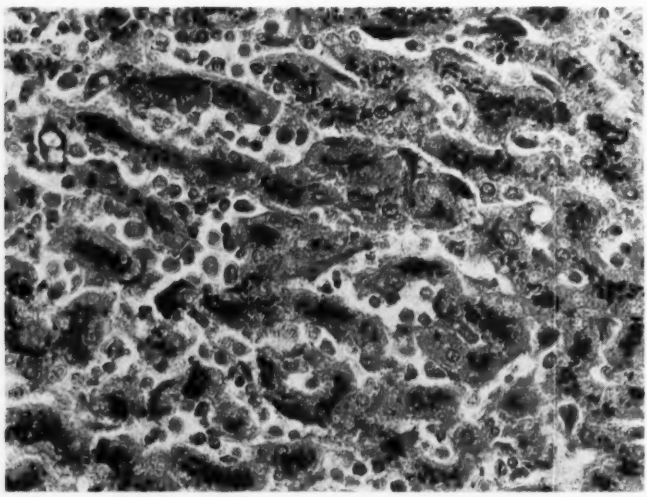

Fig. 2. (Case 6). Section of liver. (Iron stain, Berlin-blue reaction; x350).

TABLE 3

ACTUAL AND ESTIMATED TRANSFUSION REQUIREMENT

Patient	*Volume of erythrocytes, ml./day*			*Transfusion requirement*	
	*Destroyed**	*Produced*	*Difference*	*Estimated no. of 500-ml. units monthly*	*Actual, from history*
1	54	2.5	51.5	5–6	3 (1500 ml.—time interval not recorded)
2	42	14	28	3	500 ml. every 10-14 days
3	85	30	55	6	500 ml. every 5 days
4†	25	4	21	2	1500 ml. from Jan. 20 to Feb. 15, 1960
5	29	38	+9	0	0
6	45	6	39	4	1000 ml. every 2 wk.
9	7	23	+16	0	11-12 units of 500 ml. each in 6 mo. Blood loss in stools
12	40	47	+7	0	0
13	16	32	+16	0	0

*Blood volumes used in calculations were on the basis of 70 ml per kilogram of body weight except for patient 12. For that patient a Congo red blood volume was used.
†Before remission.

Chronic Lymphocytic Leukemia.—One man and two women were investigated (Table 2). Their ages ranged from 46 to 64 years. For patient 14 only the plasma iron turnover was calculated. Patients 12 and 13 were studied for 11 and 14 days, respectively. Patient 14 had a hemoglobin value of 8.4 gm.; the other two patients were not significantly anemic. The erythrocytes showed no hypochromasia, and all the serum iron values were within the normal range. The Fe^{59}-erythrocyte incorporation was normal, and there was no evidence of increased hemolysis as measured by Cr^{51}-disappearance rates.

Loss of Blood in Stools.—Twenty-four-hour stool collections were made throughout the period of observation for all patients undergoing the dual isotopic studies except patients 8, 10 and 12.

The blood loss (Table 2) was calculated on the basis of the Cr^{51} method and is expressed as the daily average. Only patients 1 and 9 had values above the normal range of 5 ml (23). Patient 9 who had chronic granulocytic leukemia has been discussed; gastrointestinal bleeding was considered a significant factor in the anemia of this patient. In patient 1 the loss of blood seemed less important.

Significant hemolysis occurred even after correction for bleeding, and the erythropoietic response was suboptimal. There was no evidence of hypochromasia on the peripheral blood smear in this patient.

In acute leukemia in our series, gastrointestinal bleeding could not be invoked as a prime etiologic factor in the mechanism of the anemia.

Bone Marrow Differential Counts.—No correlation was found between the percentage of normoblasts in the smear preparation of the bone marrow and any of the radioisotope data (Table 2). This was not entirely unexpected. In the first place the bone marrow aspirated may not be a representative specimen of the whole marrow, because the leukemic process may affect certain areas more than others. Secondly, the volume of bone marrow may be increased in leukemia (24, 25); thus, although the percentage of normoblasts in a given volume may be reduced, the total number in the whole marrow may be normal or increased.

ACTUAL AND CALCULATED BLOOD TRANSFUSION REQUIREMENT

Since many of the patients studied had required blood transfusions, an attempt was made to assess the blood transfusion requirement of each patient by balancing data on blood destruction against data on blood production. The clinical condition of the patient had to be steady in order to reach a reasonable estimate. We, therefore, excluded patients 7 and 8 because they were in the acute terminal phase of chronic granulocytic leukemia, patient 10 because of a recent massive hemorrhage, and patients 11 and 14 because complete calculations were not possible. The results in the remainder of the patients are presented in table II.

Calculations were made as follows:

1. *Destruction of Erythrocytes.*—

$$\frac{\text{Whole-blood volume in ml} \times \text{Hematocrit value}}{100} = \text{Volume of packed erythrocytes in ml}$$

$$\frac{\text{Volume of packed erythrocytes in ml}}{100} \times (\text{Per cent } Cr^{51} \text{ disappearance per day} - 1 \text{ per cent}) = \text{Ml of packed erythrocytes hemolyzed daily.}$$

The estimated (26) Cr^{51}-elution rate is 1 per cent (approx.), and this value is subtracted from the percentage Cr^{51} disappearance in the above formula. The blood volumes used in the calculation for table 3 were calculated on a basis of 70 ml per kilogram of body weight.

2. *Production of Erythrocytes.*—

$$\text{Plasma iron turnover (mg/24 hr.)} \times \frac{\text{Per cent of } Fe^{59}\text{-Erythrocyte incorporation}}{100} = \text{Erythrocyte iron turnover. (mg/24 hr.)}$$

It has been estimated (27) that there is 1.15 mg. of iron in each milliliter of packed erythrocytes. Therefore, the volume of erythrocytes (ml) produced daily

$$= \frac{\text{Erythrocyte iron turnover}}{1.15}.$$

Such calculations are obviously subject to error. Table 3 nevertheless, indicates a broad measure of agreement between the actual and estimated blood transfusion requirements except for patient 9 who was bleeding from the gastrointestinal tract. Only one of the patients who showed an excess of erythrocytic production over destruction required blood transfusion.

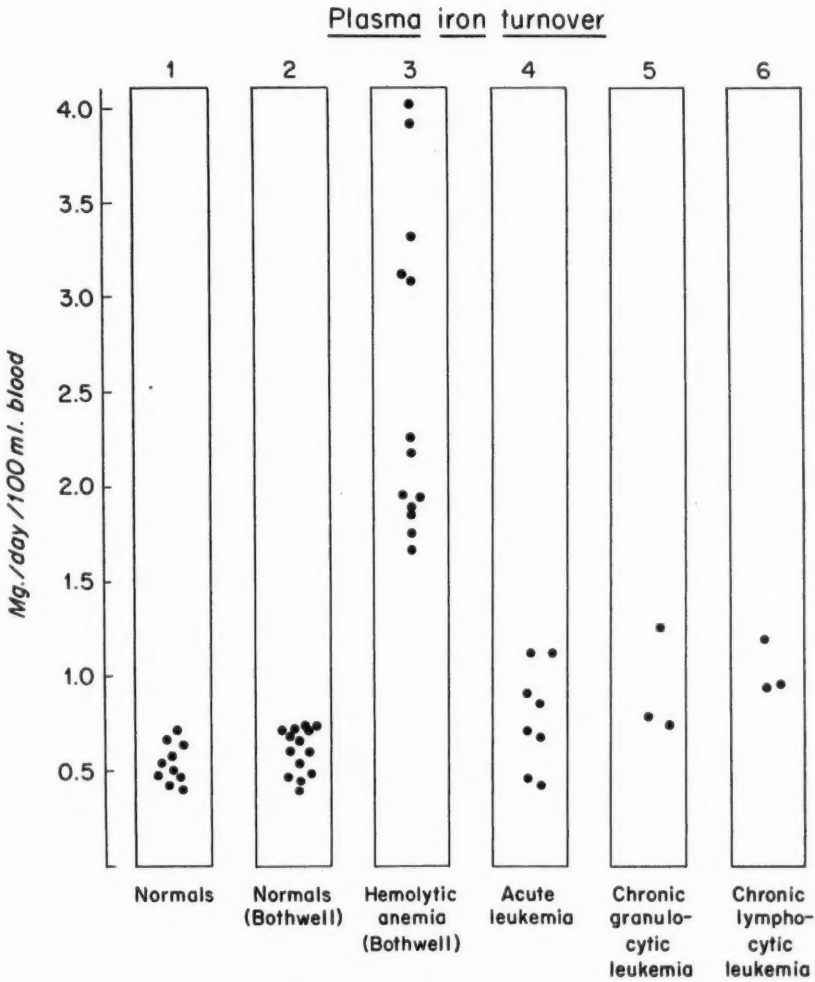

Fig. 3. Plasma iron turnover in milligrams per day per 100 ml of blood.

TABLE 4

PLASMA VOLUMES BY Fe^{59} METHOD

Patient or case	*Type of leukemia*	*Plasma volume, ml./kg.*	*Blood vol. calculated from plasma vol., ml./kg.*
1	Acute lymphoblastic	46	61
2	Acute lymphoblastic	47	70
3	Acute lymphoblastic	42	61
4	Acute lymphoblastic		
	Before remission	38	44
	During remission	37	49
5	Acute myeloblastic	48	72
6	Acute myeloblastic	84	114
7	Acute terminal stage of chronic granulocytic	59	97
8	Acute terminal stage of chronic granulocytic	67	124
9	Chronic granulocytic	87	119
10	Chronic granulocytic	68	95
11	Chronic granulocytic	37	61
12	Chronic lymphocytic	28	55
13	Chronic lymphocytic	36	57
14	Chronic lymphocytic	62*	85

*Plasma (not whole blood) tagged with Fe^{59}.

COMMENT

No attempt was made to group the cases of acute leukemia by type, because the patients had many characteristics in common, and morphologic distinction is often impossible. The plasma iron turnover rate was within the normal range, or slightly increased, in all eight patients with acute leukemia, and seven showed evidence of an increased rate of destruction of erythrocytes. According to Bothwell and associates the plasma iron turnover can be taken as an index of erythropoiesis, and in the maximal response of a normal marrow (as in hemolytic anemias) this value has been reported to show a three to sixfold increase (6). In figure 2 the plasma iron turnover in the leukemia group is compared with that of the normals and of Bothwell's patients with hemolytic anemia. The range of plasma iron turnover in our control series was the same as in Bothwell's series. In no patient with acute leukemia was the plasma iron turnover rate increased to significantly more than twice the normal mean, even though destruction of erythrocytes was occurring at an increased rate and the patients were anemic. We concluded, therefore, that erythropoiesis was suboptimal in all the cases of acute leukemia studied.

Elaborating on the suggestion of Hirschfeld, Wetherley-Mein and associates (12) postulated that the anemia of leukemia is a combination of reduced erythropoietic potential and increased hemolysis. They suggested an initial phase of partial erythropoietic failure and a later phase of excessive hemolysis. The results of the present study agree with this concept and are also in accord with clinical experience. It is common to see the patient with acute leukemia who requires

repeated transfusions of blood. This is explained on the basis of an increased rate of hemolysis, with failure of the bone marrow to respond to this stimulus. Furthermore, when a patient with acute leukemia becomes more anemic, further increase in the rate of hemolysis probably is the cause.

In our two patients with acute leukemia in whom in vivo and postmortem data were obtained, most of the Fe^{59} had accumulated in the liver. Intracellular deposits of hemosiderin were found in fixed sections and imprint preparations of liver (Fig. 3), but both patients had received many blood transfusions. The rapid rise of the external count of Fe^{59} over the liver suggests primary deposition of iron in the liver, without previous incorporation into erythrocytes. The fact that erythropoiesis was suboptimal further supports this view. Nathan and Berlin (11), however, considered that some of the hepatic iron is first taken up by the bone marrow (even when erythropoiesis is absent) and is secondarily deposited in the liver. Elmlinger and co-workers (8) also reported an abnormal accumulation of Fe^{59} in the livers of their patients with acute leukemia. The present study is believed to be the first in which primary deposition of radioiron in the liver has been demonstrated in vivo and at postmortem in the same patient.

General conclusions cannot be drawn concerning the mechanism of anemia in chronic granulocytic leukemia. In patient 9, the anemia could be at least partially explained by iron deficiency from blood lost in the stool. In patient 10 a recent acute hemorrhage made interpretation of data difficult. Neither of these patients showed evidence of hemolysis. Both had low Fe^{59} incorporation into erythrocytes, which suggests depression of erythropoiesis since under ordinary circumstances high Fe^{59} incorporation into erythrocytes is noted in iron deficiency anemia and after acute loss of blood. These two patients also had high plasma volumes (Table 4) and, as suggested by other workers (27), there may be an element of hemodilution in the anemia of this disease. Five out of the seven patients with acute and chronic granulocytic leukemia (table 4) had had high plasma volumes.

In the chronic lymphocytic leukemia group, patient 14 alone was anemic (Table 2) but only the plasma iron turnover was investigated. This was found to be slightly above the normal range. Patients 12 and 13 were not anemic. Their results revealed high plasma iron turnovers, normal Fe^{59} erythrocyte incorporation, and normal erythrocyte survival.

SUMMARY AND CONCLUSIONS

The anemia in 14 cases of leukemia was studied with combined radioiron and radiochromium technics.

Acute Leukemia.—The data obtained in the eight cases of acute leukemia support the following views and observations:

1. Anemia occurs in acute leukemia because the bone marrow is unable to compensate for the increased destruction of erythrocytes.

2. Blood loss in the stools is not a significant factor in the production of the anemia.

3. The in vivo and postmortem studies in two cases gave evidence of primary deposition of iron in the liver.

4. Treatment with an antimetabolite restored to normal the erythrokinetics in one case of acute leukemia.

Chronic Granulocytic Leukemia.—Evidence of impaired erythropoiesis was found in two of the three cases of chronic granulocytic leukemia. In two cases of chronic granulocytic leukemia the plasma volumes were high. This suggests that there may be an element of hemodilution in the anemia of this disease.

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Announcement

"Viruses, Nucleic Acids, and Cancer" will be the subject of the 17th Annual Symposium on Fundamental Cancer Research sponsored by The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. The dates of the meeting will be February 20, 21, and 22, 1963, according to Leon Dmochowski, M.D., Ph.D., Chairman of the Symposium Committee, and Chief, Section of Virology and Electron Microscopy at M. D. Anderson Hospital.

The sessions of the Symposium will relate to: structure of viruses; replication of viruses; biochemistry of virus-infected cells; properties, structure, and mode of replication of viral nucleic acids; early changes following viral infections; avian viruses and neoplasia; viruses and interferon; biological aspects of tumor induction by viruses; and interrelationship of viruses, intracellular and extracellular factors in neoplasia.

Proceedings of the Symposium will be published in a volume entitled *Viruses, Nucleic Acids, and Cancer.*

Information regarding the 17th Annual Symposium on Fundamental Cancer Research may be obtained by writing to:

Publications Department
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Texas Medical Center
Houston 25, Texas

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The Use of Iodine-132 to Study Thyroid Function Following Therapy With Iodine-131[1]

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INTRODUCTION.

A method for the direct measurement of thyroid function soon after I^{131} therapy for hyperthyroidism would be desirable. Aside from its possible use in studying the mechanism of radiation-induced changes in thyroid function, such a method might prove helpful in treating patients with I^{131} if it could predict clinical response to therapy.

I^{132} is well suited for the purpose because of two properties: (a) Gamma rays emitted by I^{132} are of higher energy than those from I^{131}, allowing the detection of the former isotope *in vivo* in the presence of even large quantities of I^{131}, and (b) the 2.3 hour half-life of I^{132} permits tests to be repeated in the same patient with relatively little additional radiation exposure to the thyroid. The tissue exposure to the gland from I^{132} is 1/50th to 1/100th of that from an equal dose of I^{131} administered(1).

The present report is concerned with a description of a practical method using I^{132} for the measurement of thyroid uptake in patients soon after therapy with I^{131} and the application of this technique in six patients.

METHODS.

Iodine-132 was obtained from a Tellurium-132 generator supplied by Brookhaven National Laboratories. The generator has been described previously(2). A 10 millicurie Te^{132} unit supplied enough I^{132} for this study for approximately three

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[1]Presented, in part, at the Eighth Annual Meeting of the Society of Nuclear Medicine, Pittsburgh, Pennsylvania.

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The views expressed are those of the authors and do not necessarily reflect those of the Naval Service at large.

weeks. The product is carrier-free and is diluted with water before administration to patients. The yield of I^{132} at each milking can be predicted from the decay curve of Te^{132}, T½ = 3.2 days, provided an interval of at least 12 hours elapses between milkings. When the generator is milked daily, contamination of the product with I^{131} (from Te^{131}) is less than 0.3 per cent.

The pulse height spectra of I^{131} and I^{132} are shown in Fig. 1. Twenty-nine per cent of I^{132} disintegration yield gamma rays of energy greater than 1 Mev. In contrast, none of the I^{131} photons is above this energy level. The method used in the present study takes advantage of this difference in spectra.

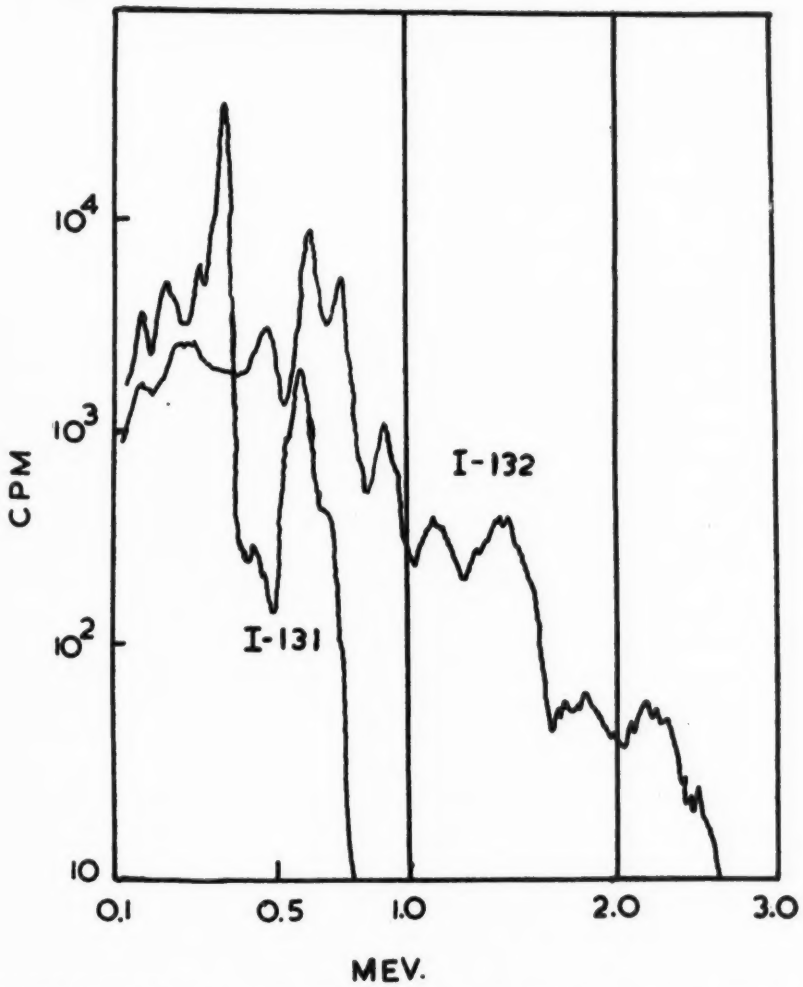


Fig. 1. Pulse Heights Spectra of I^{131} and I^{132}. On the ordinate are shown the counts per minute at various energy levels given on the abscissa.

Collimation.

Because of the high energy of the gamma rays to be counted, a heavier-than-usual lead collimator was required. (Fig. 2.) The accompanying response curve was obtained with a small source (I^{132}) at 20 cm from the face of the detector. The effectiveness of the collimator was such that the count rate at the sides was less than one per cent of the count rate at the same distance directly beneath the probe.

Pulse Height Analyzer.

Four routine diagnostic tests (in patients who have not received I^{131}) the 0.670 Mev photon of I^{132} is utilized. The window of the analyzer is centered on this "photo peak." For the purpose of this study, however, the baseline of the pulse height discriminator was set to reject all pulses corresponding to photons less than 1 Mev in energy. No upper discriminator level was used.

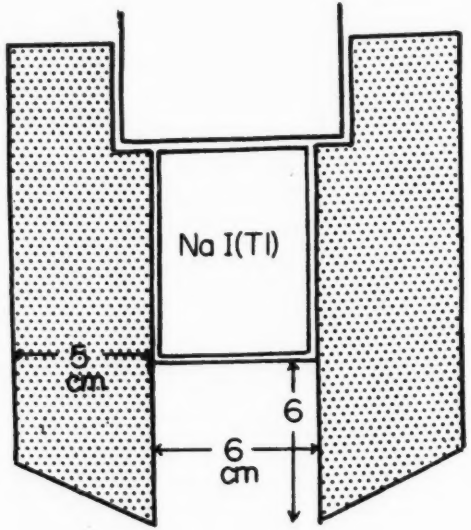
In Vivo Counting.

In the present study, doses of I^{132} ranging from 50 to 200 microcuries were given by mouth to patients and to normal volunteers who had been fasting for at least six hours.

At carefully timed intervals of one and two hours following I^{132} administration, counts were obtained over the neck and over the right thigh, at a point 10 cm from the upper edge of the patella. The skin to crystal distance was 20 cm. The left leg was positioned so that the knees were at least 40 cm apart. Residual I^{131} radioactivity in neck and in thigh was determined before administration of I^{132} in those individuals who had received I^{131} therapy.

The ratio of the net counting rates over the neck and over the thigh, at two hours following the oral dose, correlates closely with thyroidal iodide clearance, according to Myant and Pochin[3]. The neck-thigh ratio is particularly suited for this study since the filter method of correcting for extra-thyroidal neck activity would not be possible considering the high energies of the gamma rays involved.

Four women and one male with diffuse toxic goiter and a female patient with a toxic nodule were studied before and after I^{131} therapy. The diagnosis in each was established on the basis of independent clinical evaluation by two physicians and by 6 and 24-hour I^{131} thyroid uptakes and thyroid scintiscans. No antithyroid drugs or stable iodine were administered to the patients, although small doses of reserpine (0.5 mgm per day) were given for symptomatic relief, as is customary in this clinic. I^{132} studies were done immediately prior to I^{131} therapy and at approximately weekly intervals following therapy in all six patients. At each visit, careful assessment was made of clinical response, serum PBI^{127}, erythrocyte uptake of triiodothyronine, and recording of ankle reflex.



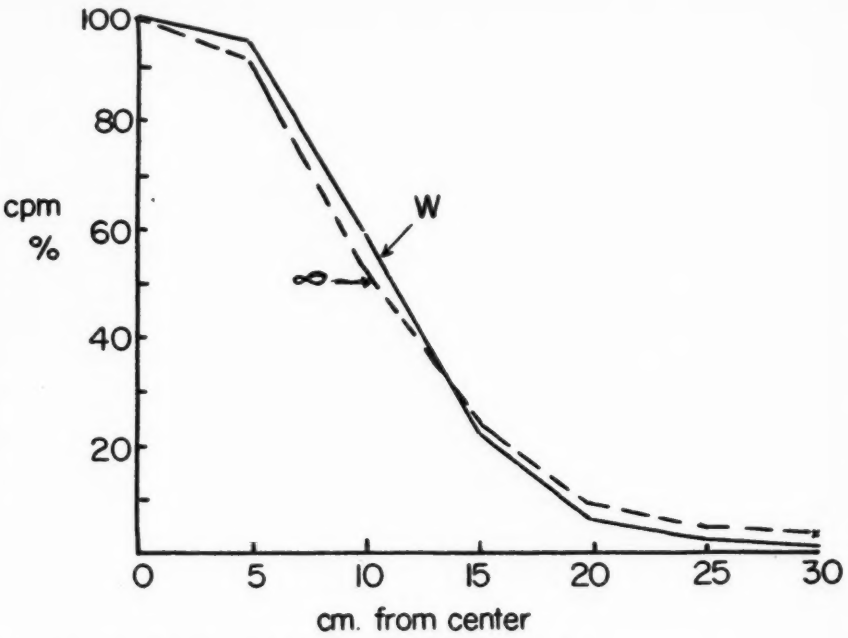


Fig. 2 (Left). Diagrammatic cross-section through special cylindrical collimator. Lead is shown by stippled area.

Fig. 2 (Right). Response curve obtained using a small source of I^{132} situated on a plane 20 cm from the detector. Ordinate is in per cent of the count rate obtained directly below the detector. Solid line (W) represents the response obtained using a single-channel analyzer, the window of which was adjusted to record photons whose energy was between 640 and 700 Kev. Broken line (∞) gives response with base line voltage set to count all pulses above 1 mev.

Thiocyanate release tests were done in five patients at various times following radioiodine therapy. One gram of potassium thiocyanate, dissolved in water, was given by mouth immediately after the 2-hour I^{132} counts. Radioactvity in the neck and in the thigh was again measured at 30 to 60 minutes after the administration of the thiocyanate.

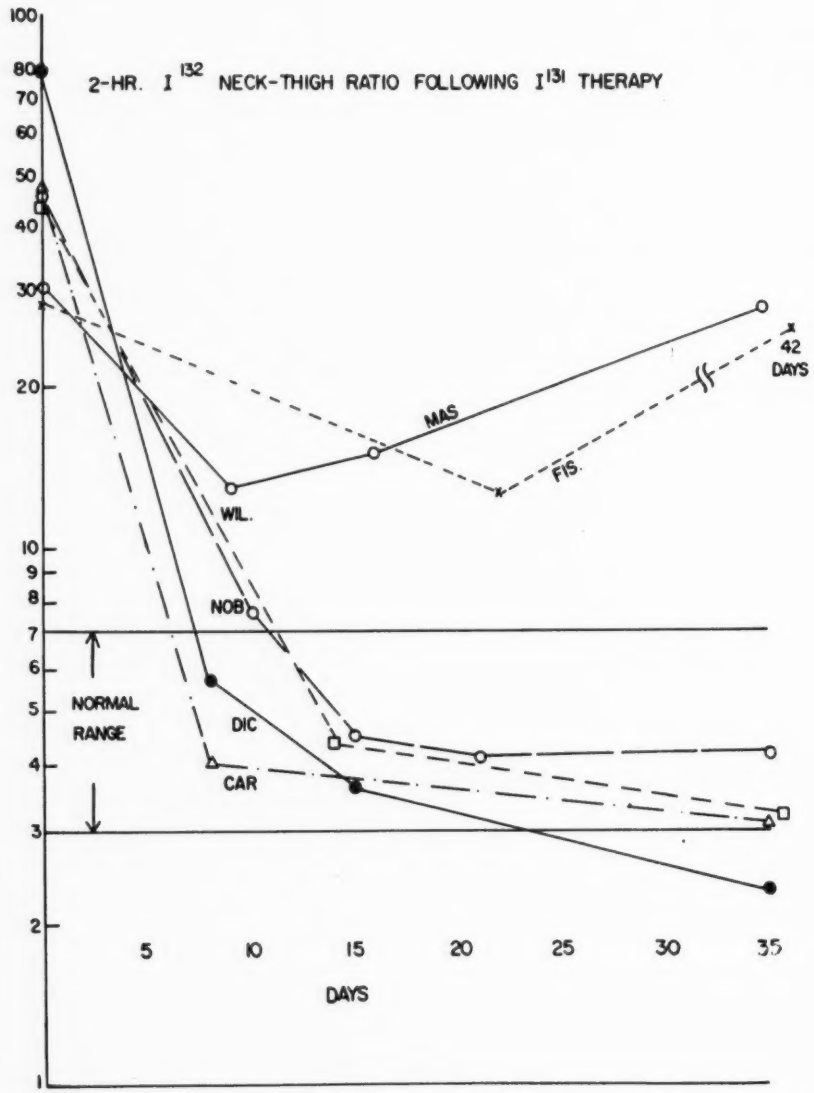


Fig. 3. Results of 2-hour I^{132} neck-thigh ratio determination in six hyperthyroid patients before and at intervals following I^{131} therapy.

Therapy doses of I^{131} varied from 4.0 to 6.0 millicuries, depending on estimated thyroid gland size and on the 24-hour uptake at the time of treatment. An effort was made to achieve a concentration in the gland of 80 μc per gram at 24 hours following the dose.

RESULTS.

Among eighteen euthyroid individuals of both sexes, the mean 2-hour neck-thigh ratio was 4.23 ± 1.25, the individual values ranging from 2.7 to 6.6. In the group of fifteen untreated thyrotoxic patients, the results varied from 13 to 112, with a mean of 47.6 ± 27. Thus, there was no overlap between the two groups. These results agree closely with those obtained in a larger series of subjects by Halnan and Pochin[1].

Fig. 3 gives the results obtained in the six patients who rceived I^{131} therapy for hyperthyroidism. Before treatment, the 2-hour neck-thigh ratio was elevated in each case. In four cases, each of whom had a diffuse toxic gland, the neck-thigh ratio became normal within fifteen days after therapy. These four patients went on to show clinical improvement at three to six weeks. Patients Car, Nob, and Wil, were considered to be in a normal metabolic state at three months and re-

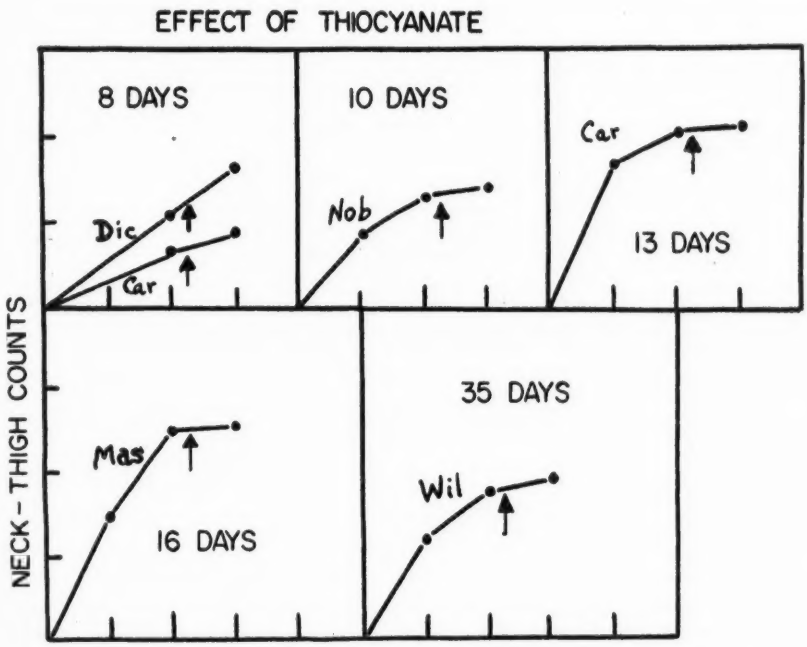


Fig. 4. Results of thiocyanate release tests performed on five patients at various intervals from eight to thirty-five days following I^{131} therapy. Abscissa is time, in hours, following ingestion of I^{132}. One gram KSCN was given immediately after the two-hour counts. Ordinate gives I^{132} counts over the neck minus the counts over the thigh.

mained so, at last visits (six to eight months). Patient Dic, however, eventually became myxedematous and still requires small doses of thyroid replacement therapy at seven months post-therapy.

In contrast to these, two other patients showed smaller, transient reductions in the neck-thigh ratio. Patient Mas was a case of recurrent hyperthyroidism treated eight years previously with propylthiouracil for six months. Following radioiodine therapy, she exhibited an unusually delayed, incomplete clinical response, so that at the last visit, four months post-therapy, symptomatic improvement was just beginning.

Patient Fis was the one case in the group with a toxic nodule, demonstrated by scintiscan. As seen in Fig. 3, the fall in neck-thigh ratio was slight and temporary in her case. After a transient period of remission, she relapsed and required a second treatment drink at four months. At this time, a repeat I^{131} thyroid scintiscan showed a diffuse pattern of activity (24-hour uptake = 84 per cent of dose).

Fig. 4 gives the results of six thiocyanate release tests performed on five patients at various times following I^{131} therapy. Thyroid accumulation of I^{132} was estimated by the difference between the neck and the thigh counting rates (ordinate) at one, two, and three hours following I^{132} ingestion. If a selective block were present in organification of trapped iodide within the thyroid glands of these subjects, the thiocyanate given at two hours (arrows) would have discharged some of the trapped I^{132} from the glands. As seen in Fig. 4, however, in no case was such a discharge of radioactivity from the neck observed. It would appear, then, that the rate of iodine-incorporation kept pace with iodide-trapping in these glands at least at the times when these tests were performed.

DISCUSSION.

In 1953, Myant[4] reported on the prognostic value of I^{131} tests of thyroid function after I^{131} treatment of thyrotoxicosis. He was able to estimate the neck-thigh ratio using large (100 to 500 μc) doses of I^{131} as early as three weeks following therapy. He observed that a clinical remission usually did not occur unless there was a significant depression of thyroid uptake at three weeks.

Because of the high residual radioactivity present in the neck, function tests using I^{131}, even in large tracer doses, are not feasible earlier than three weeks after I^{131} therapy. Furthermore, more than one such study done on the same patient would probably add significant additional radiation to the thyroid gland.

In an attempt to avoid these difficulties, Thomas and co-workers[5] have developed a technique of estimating thyroidal iodide uptake (or clearance) by measuring changes in the urinary excretion of the therapy dose itself during and after thyroid blockade with potassium perchlorate.

In a preliminary report[6] these investigators, using this indirect method, found a significant reduction of iodide clearance as early as five days post-treatment. They suggest, on the basis of their results, that the mode of response in the first twenty-eight days may be helpful in predicting utlimate clinical results of I^{131} therapy.

Their indirect method, however, is technically complex and involves certain basic assumptions. Nevertheless, it is heartening to find that our results using I^{132} are in general agreement with those obtained by Thomas and co-workers. The latter investigators have used their technique in developing a system for radioiodine therapy. We suggest that the I^{132} method described here offers a simpler, more direct approach to the same problem.

The finding that the avid accumulation of iodide by the thyroid gland in thyrotoxic patients may be profoundly reduced as early as one week after I^{131} therapy is of considerable interest. From the results of the thiocyanate tests it appears that the organification processes within the thyroid are not as seriously affected as the earlier (iodide) phase. In analyzing the radiation effect, therefore, let us consider those factors which might be responsible for these early changes in thyroid iodide uptake.

The radiation-damaged thyroid gland releases for a time increased amounts of stored hormone. In the presence of an intact anterior pituitary-thyroid axis, one would expect the thyroid to be indirectly suppressed under these conditions. However, in general, thyrotoxic patients do not show such suppression when exogenous thyroid hormone is supplied. Hales, et al.[7] have recently shown that suppressibility usually returns when the radioiodine-treated patient becomes clinically euthyroid. The early decline in neck-thigh ratio observed in the present study occurred while the patients were still thyrotoxic. It would appear, therefore, that an idirect mechanism involving the pituitary is not a likely explanation.

It is more probable that the inhibition of thyroid iodide accumulation results from a direct radiation effect on the gland. Data are very sparse regarding histologic changes in the toxic thyroid soon after I^{131} therapy. Vickery[8] in a study of thyroid biopsies obtained from 19 days to eight years following radioiodine treatment for hyperthyroidism, emphasized the variation in pathologic effects from area to area, even within the same follicle. Details are not given, however. Studies on the morphologic changes in normal thyroid after ablative doses also indicate a great variation in distribution of radioiodine within the gland[9,10]. Obviously, the spatial distribution of radioiodine in toxic thyroids would be an important factor in determining the effect of treatment.

It is not surprising to find radiation-induced effects on thyroid function in the first week or two following treatment even before morhphologic damage becomes evident. Most of the total radiation is delivered to the gland within the first week or ten days following I^{131} therapy.

The observed inhibition of iodide accumulation by the thyroid during the first two weeks post-therapy may be due to an effect on any or all of the factors influencing thyroid clearance. The rate of blood flow through the gland and the iodide "trapping" mechanism both affect clearance[11]. It seems possible that at least part of the radiation effect may involve an acute reduction in thyroid blood flow. In order to settle this point, direct measurement of thyroid blood flow in thyrotoxic patients would be necessary.

ACKNOWLEDGMENT

We wish to acknowledge the technical assistance of B. R. Creech, HMC, USN, and M. S. Breen, HM2 USN

ADDENDUM

After this paper was submitted for publication, a report by Einhorn and Hastad appeared (12) in which the thyroid uptake of I^{132} was determined in forty-one patients following I^{131} therapy. Although the earliest uptake determination was done three weeks following treatment, the patterns of response were similar to those obtained in our study.

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Calibration of Thyroid Uptake Systems

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A survey of thyroid uptake facilities (1) conducted by the Medical Division, Oak Ridge Institute of Nuclear Studies, demonstrated considerable variation of uptake values in different laboratories on the same mannequin subject. The survey was conducted using mannequins to simulate the uptake patients.

Given the same subject, results of thyroid uptake measurement in different laboratories show great variation. Percent uptake reported does not correlate with the true accumulation by the thyroid. However, there is presumably clinical reliability in the relative values obtained in any one laboratory. This variation among laboratories is well documented (2) (3) (4) (5). Standardization is achieved by correlating the thyroid status in clinical cases with the percent uptake determined in that laboratory; there is thus established a range for hypothyroidism, euthyroidism and hyperthyroidism for each laboratory.

The results of the mannequin survey and the extreme variance in published ranges of normal uptakes prompted a comprehensive analysis of the physics of uptake measurement systems by Brucer (6), who proposed a new (physical) technique for the measurement of thyroid uptake of iodine. A standardized method should yield values reasonably close to the actual amount of isotope in the gland and permit establishment of ranges of values for patients that would be valid in all laboratories.

The immediate problem in laboratories with established clinical correlation of uptake results is the conversion of these results to equivalent values in the standard method. It would be desirable to have a physical technique which would indicate the change in ranges of normal and abnormal from any clinically employed method of uptake measurement to the ranges of normal and abnormal in the standardized method. This would obviate the necessity of subjecting large groups of patients to radiation studies for standardization purposes,

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[2]From the departments of biophysics, medicine and biochemical research, Touro Infirmary and Tulane University, New Orleans, Louisiana.

conserve time in the clinical laboratory and prevent interruption in service. A physical conversion technique has been proposed and tested; it requires the use of a patient simulant of known and variable parameters.

THYROID UPTAKE CALIBRATION KIT (TUCK)[1]

TUCK (Figure 1) is a simulated I^{131} thyroid uptake patient in which uptake can be changed in controlled steps. The purpose of the mannequin is to provide a system of pre-determined variation of uptake values and give an evaluation of the validity of the *percent* uptake and the linearity of the method. Thus a calibration curve is provided for correcting data from an existing method of uptake to true percent uptake or to equivalent values in some other method.

Description

TUCK-10 is a hollow lucite cylinder of approximately the same external dimensions as the ORINS standard neck phantom. A hole is provided for test tube samples in the same relative position as the hole in the ORINS phantom. The cylinder is filled with an ion exchange resin impregnated with enough mock iodine Cs^{137}-Ba^{133} (7) to provide a background count equivalent to the back-

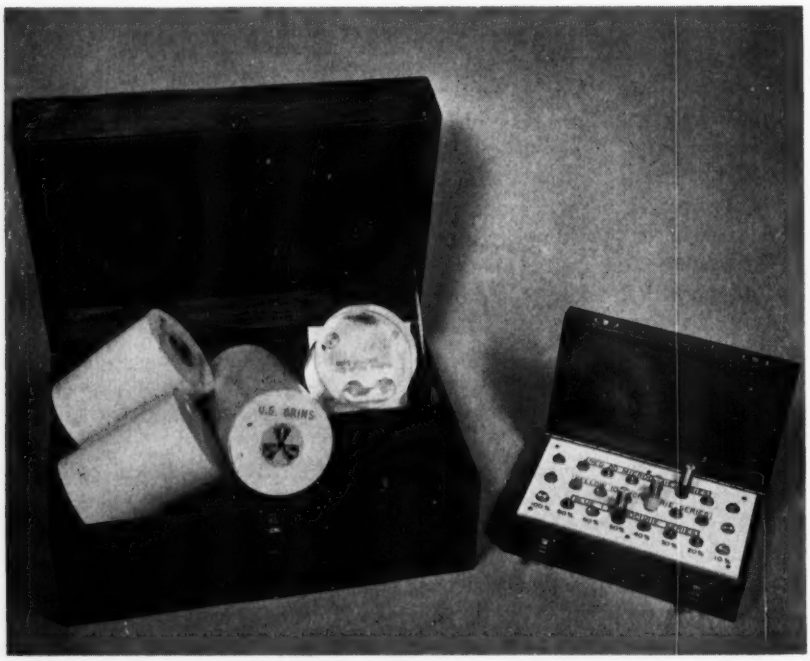

Fig. 1. TUCK, Thyroid Uptake Calibration Kit.

[1]Constructed at the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission.

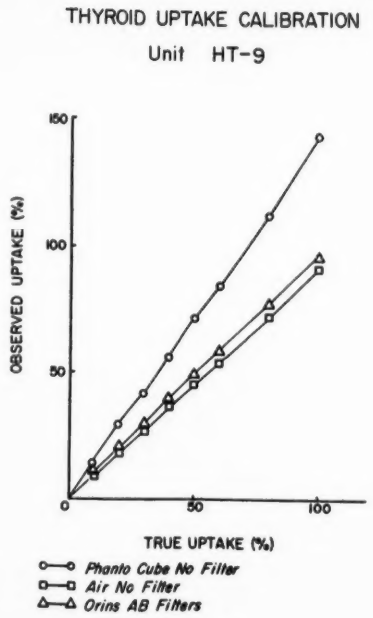

Fig. 2

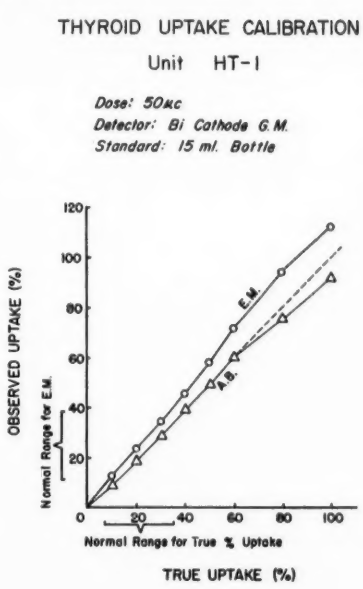

Fig. 3

Fig. 2. Calibration Curves from Uptake System (HT-9) Using TUCK.

Fig. 3. Calibration Curves from Uptake System (HT-1) Using TUCK.

Legend: E.M.—Existing Method.
A.B.—AB Method.

ground in a typical normal patient who has been given 10 μc. NaI^{131}. TUCK-50 provides a body background count equivalent to the background in a typical normal patient who has been given 50μc. NaI^{131}. Three sets of metal containers are provided with quantities of mock iodine on resin to simulate 100, 80, 60, 50,

TABLE 1

CALIBRATION DATA FROM UPTAKE SYSTEM (HT–9) USING TUCK

Tube %	*Existing Method (Phantocube)*	*Existing Method (Air)*	*AB Method (ORINS)*
100	145	92	96
80	113	73	78
60	85	55	57
50	72	46	49
40	57	37	39
30	42	27	29
20	30	19	20
10	15	10	11

TABLE 2

CALIBRATION DATA FROM UPTAKE SYSTEM (HT–1) USING TUCK

Uptake	*Existing Method*	*AB Method*
	percent	*percent*
Low	0–10	0–8
Normal	11–39	9–33
Borderline	40–44	34–37
High	45–100	38–100

40, 30, 20 and 10 per cent of the administered dose for three different doses of 50, 10, and 1 microcuries. An ORINS standard neck phantom and another cylinder called TUCK-body complete the kit. The TUCK-body is filled with mock-iodine impregnated resin at the same concentration as TUCK-50. This provides additional body background distribution necessary to test system collimation. Assembly is as follows:

1. TUCK-body is placed in the vertical position.
2. TUCK-10 or TUCK-50 is placed on TUCK-body.
3. Appropriate source sequence is serially placed in TUCK-10 or TUCK-50 and counted. Determinations for each source are made in the same manner as for a patient by each method to be tested or compared. The 100 percent tube must be counted as the dose standard with the existing equipment in the established way. If comparison with some new method is to be made (such as the AB method with ORINS phantom), the tube must also be counted in the appropriate way for this method. Uptakes are calculated for each tube in TUCK. The observed uptake is plotted against true value or uptake on an existing method is plotted against uptake on a new method. An example follows:

Clinical Laboratory Calibration (Unit H T-9)

Laboratory Equipment: Scintillator (small crystal), scaler, Phantocube®.

Existing Laboratory Method: Uptake measured 24 hours after administration of 10 μc NaI^{131} capsule. No filters were employed. Room background was subtracted from thyroid counts and standard counts (in Phantocube®).

TUCK assembly: TUCK-10, TUCK-body, 10 μc source sequence, ORINS Standard phantom.

The uptake values of TUCK were measured by the existing method and by the AB method with ORINS neck phantom. The uptake values by the existing method were also measured with the standard counted in air.

The results of this calibration are shown in Table 1 and Figure 2.

It has been shown by Brucer (6) that the gamma spectrum of an I^{131} source in the ORINS standard neck phantom is the same as that emitted by a patient. The spectrum of TUCK with an I^{131} source was compared with the ORINS phantom with the same source and found to be in close agreement.

The calibration method was tested in eleven radioisotope laboratories where it was possible to demonstrate and measure differences in methods and provide comprehensive calibration data. In every laboratory the uptake measured by the AB method agreed reasonably well with the known standard values. Of particular interest is the calibration data from the Biophysics Department, Touro Infirmary (Figure 3), for this is an example of a laboratory with its own range of normal uptake, based upon a carefully evaluated clinical series. The AB technique agreed with true values except for the very high uptakes. The method in use consistently gave values that were too high. Values obtained with the existing method and with the AB method were plotted and used for the preparation of a conversion table (Table 2 and Figure 3). It remained for this conversion to be demonstrated clinically.

The 24 hour uptake of a 10 microcurie dose was measured with the AB method on a scintillation detector. This was followed as soon as possible by the measurement in the same patient of the 24 hour uptake of a 50 microcurie dose with the existing method on a Bismuth-cathode Geiger-Muller detector. This method entails the counting of the patient without filters and the counting of the standard in a 15 cc. glass vial in air (3). Forty patients were studied in this

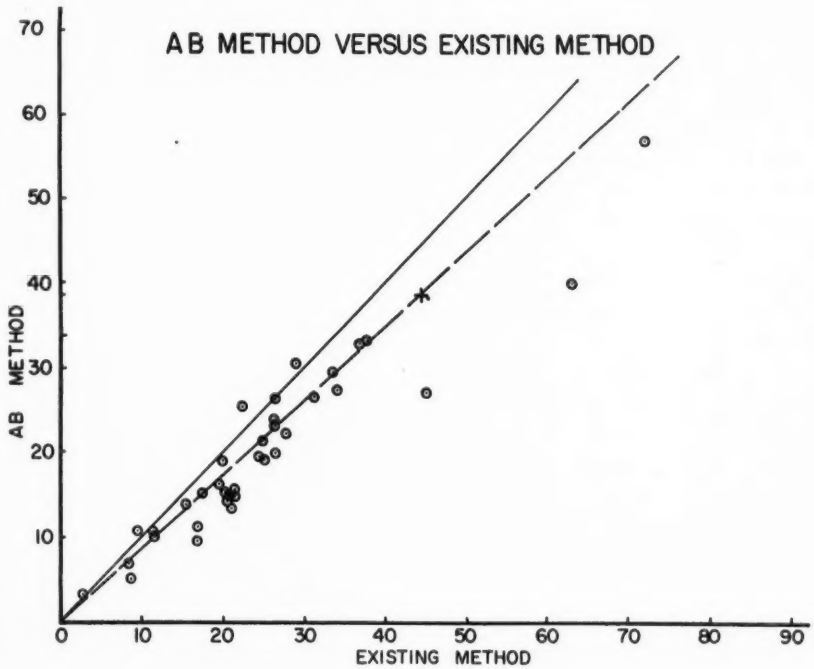

Fig. 4. Correlation of Two Methods on Two Different Uptake Systems (40 Cases).

Legend: Solid Line—45° Slope of 1:1 correlation.
Broken Line—Physical Conversion Line.

manner. The uptake values ranged from 4 to 73 percent with the existing method. The results of the two methods are plotted in Figure 4. The data agree well with the conversion line (dashed line) as obtained from the TUCK data (Figure 3). There were two exceptions. One was a toxic patient with substernal extension of the thyroid, whose AB value was falsely low due to inability of the B filter to shield completely the active thyroid tissue; there is no explanation for the other exception. The last difference between the existing method and the AB method is further demonstrated by the lack of agreement with the solid line representing a direct correlation between methods.

Comparisons were also made of two uptake values on each patient with the same detection system. One of the uptakes was done by the AB method and the other by the existing method. A bismuth-cathode G.M. detector and a 50 uc dose of NaI^{131} was used in each case. Two hundred and forty-seven unselected patient uptakes using both methods were done. The uptake for each patient by the AB method was plotted against the uptake by the existing

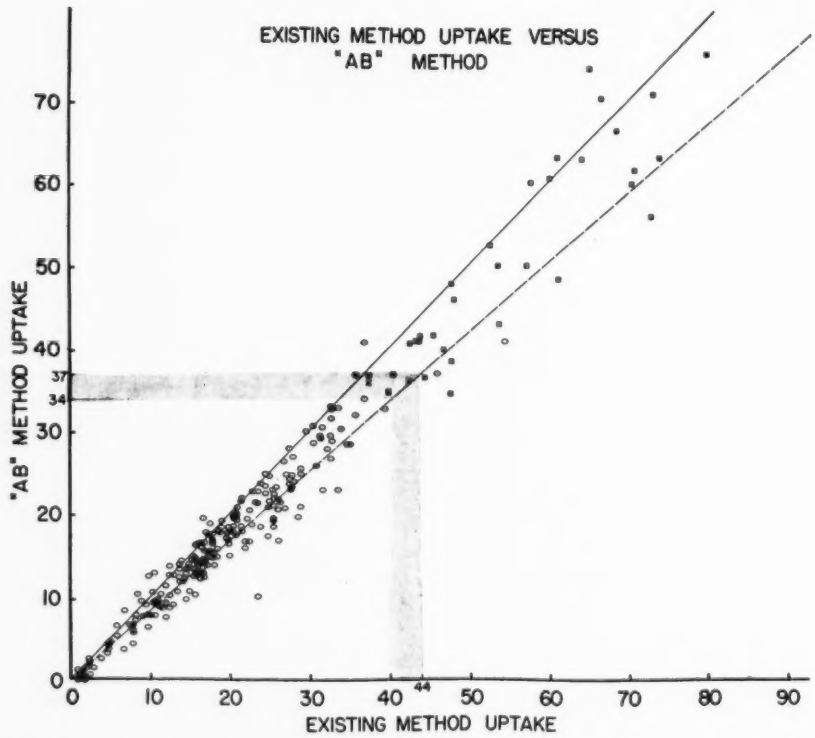

Fig. 5. Correlation of Two Methods on Same Uptake System (247 cases).

Legend: ellipses: euthyroid subjects.
squares: hyperthyroid subjects.
crosses: questionably hyperthyroid subjects.

TABLE 3

CORRELATION OF AB METHOD WITH CLINICAL STATUS (247 CASES)

AB Method Versus Existing Method					
AB Range	*Patients*	*Clinical Status*	*AB Value*	*Existing Method Value*	*Existing Method Range*
			percent	*percent*	
L–N <34%	209	NT	<34.0	<40.0	L–N
B 34–37%	8 TH	NT	36.0	46.0	H
	BE	NT	36.5	36.0	N
	AB	?T	35.2	36.0	N
	WR	?T	36.0	42.0	B
	SA	T	34.0	49.0	H
	AM	T	34.4	40.0	B
	DA	T	36.0	45.0	H
	SA	T	37.0	41.0	B
H >37%	30 20	T	>41.0	>44.0	H
	GU	T	38.0	37.0	N
	RA	T	38.0	48.0	H
	BI	T	40.0	47.0	H
	LO	T	41.0	45.0	H
	LA	T	41.0	44.0	B
	HE	T	41.0	43.0	B
	GU	T	41.0	43.0	B
	CO	T	41.0	42.0	B
	ME	NT	41.0	54.0	H
	WI	NT	41.0	37.0	N

Legend: L = low, N = normal, B = borderline, H = high; NT = non-toxic, ?T = questionably toxic, T = toxic

method (Figure 5). If the uptakes were the same by both methods, one would expect a distribution about the 45 degree line (unbroken line). The scattergram more closely approximates the line obtained by using the thyroid uptake calibration kit (dashed line).

Tables 3 and 4 compare the two methods on the basis of clinical classification of patients within the established reference frames of low through

TABLE 4

CORRELATION OF EXISTING METHOD WITH CLINICAL STATUS (247 CASES)

Existing Method versus AB Method

Existing Method Range	*Patients*		*Clinical Status*	*Existing Method Value*	*AB Value*	*AB Range*
				percent	*percent*	
L–N	213	209	NT	<40.0	<34.0	L–N
<40%		BE	NT	36.0	36.5	B
		WI	NT	37.0	41.0	H
		AB	?T	36.0	35.2	B
		GU	T	37.2	36.3	B
B	7	WR	?T	42.0	36.0	B
40–44%		AM	T	40.0	34.4	B
		SA	T	41.0	37.0	B
		CO	T	42.0	41.0	H
		QU	T	43.0	41.0	H
		HE	T	43.0	41.0	H
		LA	T	44.0	41.0	H
H	27	20	T	>44.0	>41.0	H
>44%		DA	T	45.0	36.0	B
		LO	T	45.0	41.0	H
		BI	T	47.0	40.0	H
		RA	T	48.0	38.0	H
		SA	T	49.0	34.0	N
		TH	NT	46.0	36.0	B
		ME	NT	54.0	41.0	H

Legend: L = low; N = normal; B = borderline; H = high; NT = non-toxic; ?T = questionably toxic; T = toxic

normal, border-line and high uptake by each method. All 209 patients in the low through normal uptake group by the AB method (Table 3) were non-toxic. All of these patients had uptakes less than 40 percent by the existing method. Of the 213 patients in the low through normal frame by the existing method (Table 4) 211 were clinically nontoxic, one was questionably toxic and one was toxic. Within the group were 3 borderline and one high uptake by the AB method.

There were 8 patients in the borderline uptake group by the AB method (Table 3). Two were clinically non-toxic, 2 were questionably toxic and 4 were toxic. In the existing method 2 had low through normal, 3 had borderline and 3 had high uptakes. There were 7 patients in the borderline group by the existing method; one was questionably toxic and 6 were clinically toxic (Table 4). All of them showed borderline or high uptakes by the AB method.

There were 30 patients in the high uptake group by the AB method (Table 3); 28 were clinically toxic and 2 were euthyroid. One euthyroid patient was an alcoholic with a high uptake by both methods; we cannot explain the high uptake of the other euthyroid patient who had a normal uptake by the existing method. There were 27 patients in the high uptake group by the existing method (Table 4). Twenty-five were clinically toxic and two were euthyroid. One euthyroid with a toxic level uptake was the alcoholic patient (ME) referred to above; the other had a borderline uptake by the existing method.

Conclusions:

The results substantiate the validity of using the thyroid uptake calibration kit to physically interpolate a clinical range of uptake values for the AB method from another method of uptake. This has been shown with a series of patients using the same detector. Clinically established ranges can be extrapolated from one detection system to another by using the thyroid uptake calibration kit. Since percent uptake by the AB method seems in most cases to be close to the true percent uptake, the clinical reference frame should be universally applicable to any thyroid uptake.

Summary:

The conversion of an existing thyroid uptake method to the AB method is described. The ranges for the 24 hour AB method uptake are defined. Good correlation with a clinical series has been demonstrated.

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JOURNAL OF NUCLEAR MEDICINE 3:454-471, 1962

Detection of Bone Metastases in Scanning Studies with Calcium-47 and Strontium-85[1]

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INTRODUCTION

This is a report of the application of a new scanner, the HEG scanner (1), to the detection of bone metastases in patients with breast cancer where the usual radiographs had not revealed such bone lesions. In previous work, the uptakes of calcium-47 (Ca-47) in various parts of the skeleton in patients with bone lesions were studied. The observation was made that the presence of bone metastases often resulted in uptakes of Ca-47 that were larger than normal. This was observed whether the lesions were osteoblastic or osteolytic, but in particular, in cases where the lesions were progressing or healing (2, 3). These observations suggested that such elevated uptakes of calcium might be used for the detection or localization of bone metastases even before visualization on radiographs. Results of scans of the spine of one patient, whose radiographs had failed to reveal any bone metastases were also reported (3). These data demonstrated high uptakes in an area of pain, and were taken to indicate the presence of a bone lesion. In this paper further studies on this patient will be described.

Our previous work was accomplished with a conventional scintillation detector and was quite time consuming. Furthermore, only a collimator with large aperture was available which measured the uptake not only at the tumor site but also of a relatively large and varying amount of surrounding normal bone. In order to realize the unique advantages of high energy gamma ray emitting isotopes such as Ca-47, Sr-85, Zn-65, etc., and to optimize the possibility of detecting small lesions, a heavily shielded scanner was designed and built. It is

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[1]Divisions of Biophysics and Clinical Investigation, the Sloan-Kettering Institute for Cancer Research, and Memorial Hospital for Cancer and Allied Diseases, N. Y., N. Y.

Part of this material was presented at the Eighth Annual Meeting of the Society of Nuclear Medicine, Pittsburgh, Pennsylvania, June 14-17, 1961.

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equipped with a variety of collimators as well as a unique quantitative read-out system (1). Scans are presented here which show how the very detailed information obtained with a focusing collimator makes it possible to determine the size, activity and precise location of lesions.

During the progress of this work, a preliminary report has appeared describing similar studies towards detecting bone metastases in the spine using stron-

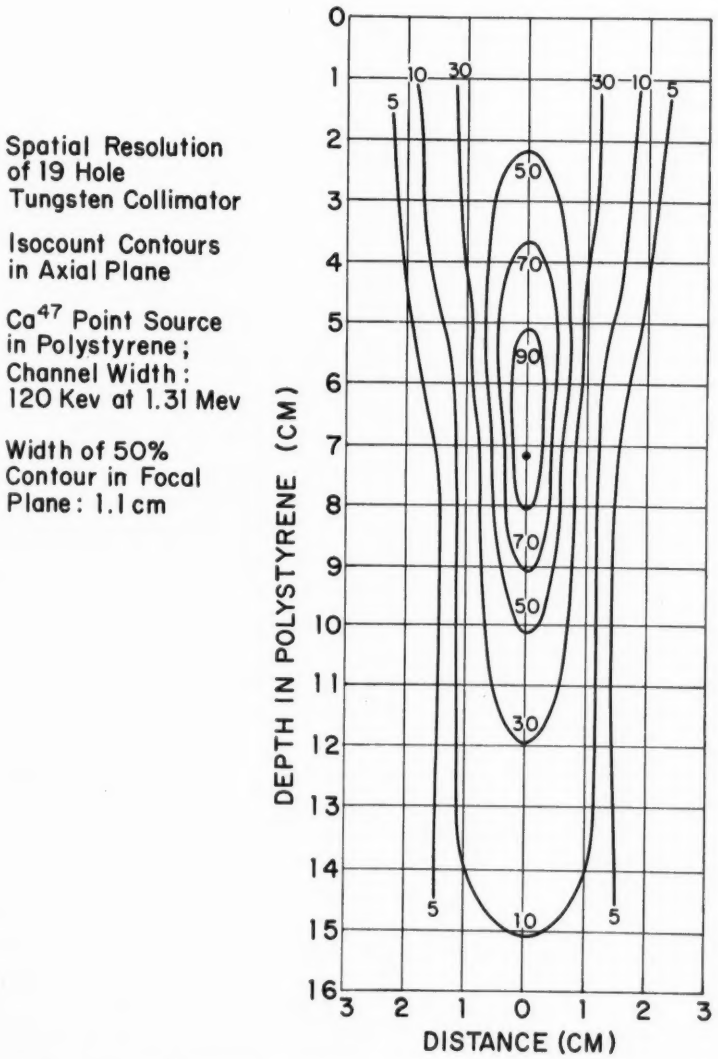

Fig. 1. Isocount curves of the tungsten 19 hole focusing collimator for a Ca-47 point source in polystyrene.

tium-85 (Sr-85) (4). This work originated from the early observations made by Bauer, et al., of elevated Sr-85 and Ca-47 uptakes in fractures and other bone lesions including high uptakes of Sr-85 in three cases of known metastatic lesions in bone (5).

METHODS

Calcium-47 was obtained by neutron irradiation of enriched calcium-46. The techniques of assay and preparation have been described earlier. The Sr-85 was obtained from Nuclear Science and Engineering in Pittsburgh. The materials were sterilized and injected intravenously in a volume of 5-15 cc saline using a calibrated syringe. The patients received about 50 uc of Ca-47 or 100 uc of Sr-85 except E.K. who received 300 uc of Sr-85. The average radiation dose delivered throughout the skeleton was estimated to be about 1-1.5 rad per 100 uc of either isotope with no allowance for excretion.

The external counting was done with the high energy gamma ray (HEG) scanner (1). It has a 4″ x 4″ NaI (Tl) crystal heavily shielded with tungsten and lead. Various collimators can be inserted in the aperture of the shield. Highest resolution is obtained with a tungsten focusing collimator (Fig. 1). Other collimators used in this study had single cylindrical apertures with 1″ and 2″ diameters. The detector is moved by servo-controlled motors in two orthogonal directions in the horizontal plane and also in the vertical plane. Counting is

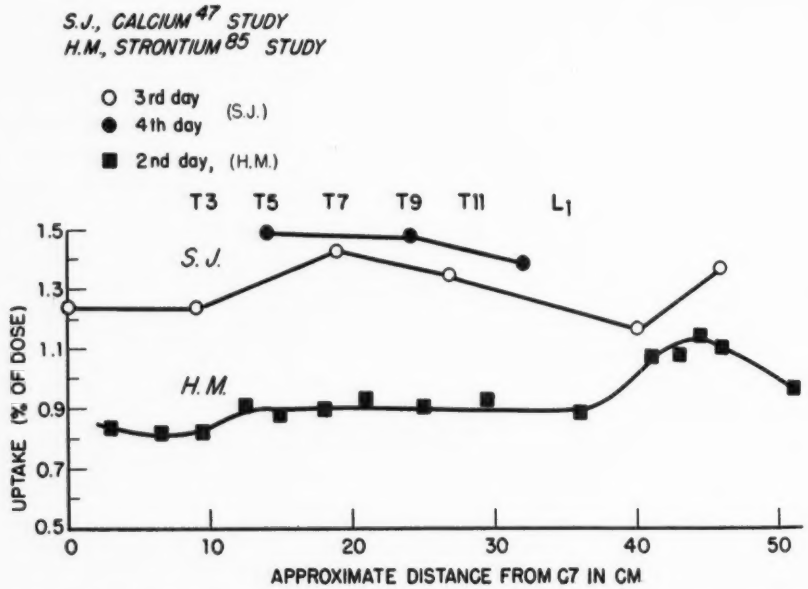

Fig. 2. Uptakes of Ca-47 and Sr-85 at various points on the spine measured with a 2″ diameter cylindrical collimator. The labeled vertebrae refer to S.J. Uptakes are expressed in per cent of the administered dose as measured with the 2″ collimator geometry and described in the text.

possible using either continuous motion, or in stationary positions. Manual control is used for stationary counts taken with the counter in contact with the skin or when counting times longer than one minute are necessary. In automatic scans preset times of from 5 seconds up to one minute can be used. At the end of each stationary position count, the result is printed out by an electric typewriter and the detector is automatically moved to the next position to be counted according to a predetermined program. In the scans presented here, 3/16″ or 3/8″ stepping was used in both horizontal directions. The typewriter carriage is driven by two synchromotors so that the two-dimensional display of counts on the paper is in 1:1 scale. Since there is adequate space for only three digits on the paper when the smallest stepping of 3/16″ is used, the three first digits in each number are printed out and any digit over a thousand is printed in red. Thus, in effect, a six digit read-out is realized. In the black and white reproduction of these red and black numbers the missing digits have been added to make the interpretation correct. Inside each collimator a small light source is fixed which throws a light

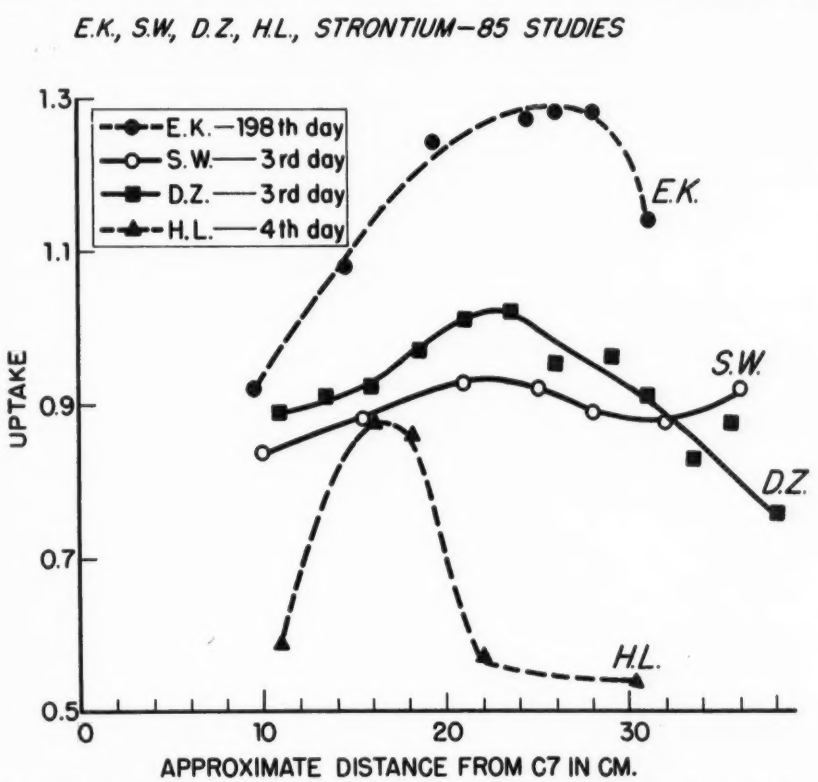

Fig. 3. Uptakes of Sr-85 at various points on the thoracic spine measured with the 2″ diameter cylindrical collimator. H.L. had complaints of pain at T6-T7 (16-18 cm from C7) and E.K. at T8-T9 (about 20-25 cm from C7). The uptakes are expressed as per cent of administered dose as measured with the 2″ collimator geometry.

spot in the direction of the center axis of the collimator on the patient's skin while scanning, and aids the making of convenient landmarks on the scan. At the end of the scan the paper is superimposed on the patient and contours and bony points are also marked on the scan. This makes it possible to superimpose the scan on radiographs, or later to relocate these same areas on the patient.

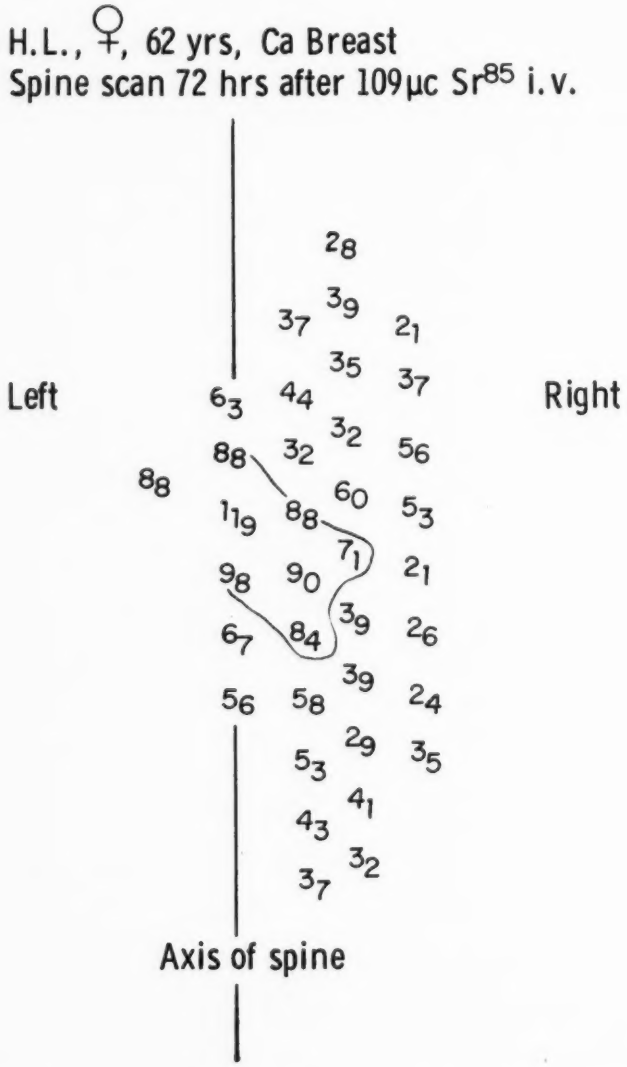

Fig. 4. Focusing collimator scan obtained with preset time of 15 seconds, background of 17 counts per 15 seconds and spacing between points of 3/8 inches.

The identification of vertebrae was sometimes difficult, and therefore after the first scan, each point of interest was identified by measuring the distance in centimeters along the spine from C7 with a tape. This distance will be somewhat different from that indicated in the automatic scans where the scanner moved in one horizontal plane.

Automatic scans were performed using either the 1″ straight hole or the focusing collimator. The patient was placed in supine position and the back made as level as possible with the help of pillows. The front of the collimator was about 1 cm away from the skin at the position of closest approach, and up to 2.5 cm from other areas. Scans over ankles and elbows were performed in the same way, making the area as level as possible. The effect on the count rate of the variations in the distance between collimator and skin was studied in patient E.K. After the completion of a scan along the spine the collimator was brought back to a position about 20 cm from C7 and counts were taken at various distances from the skin. Results expressed as percent of the maximum count rate are shown in Table 1 together with a similar set of measurements obtained over the ankle lesion in the same patient. These show that the count rate is not very sensitive to changes in the collimator skin distance which is not surprising since we are dealing with extended sources.

TABLE 1

EFFECT OF VARIATIONS OF THE FOCUSING COLLIMATOR TO SKIN DISTANCE ON THE COUNT RATE

Distance to Skin	*% of Maximum Count Rate in*	
	Vertebrae	*Ankle Lesion*
Contact	100	—
1 cm	100	—
1.5 cm	—	90
2 cm	98	—
2.5 cm	—	94
3.5 cm	98	100
4.5 cm	—	100
5.5 cm	88	96
6.5 cm	88	—

The basic survey was in all cases done manually by stationary contact measurements with a cylindrical collimator which was of 2″ diameter, except in S.J. where an older but similar detector was used (2). The counter was then positioned over each point so that the end surface of the collimator was parallel to the skin and as close as possible. In these measurements, the count to background ratios ranged from 4 to 100 and the standard error due to counting statistics was

less than 3 per cent of the net count rate (after background subtraction) except for the measurements of the tibia activity in patient H.M. where only about 600 counts were obtained in one minute. With a background of 90 counts per minute determined for 5 minutes this gave a standard error of the order of 5 per cent.

Similar technique was used in patient H.L. for additional measurements with a 1″ collimator. This was placed at 5 different positions from 5 cm below T7 to 5 cm above. The standard errors of these measurements were less than 7 per cent.

Patient E.K. had been studied for 285 days with Sr-85. The lesions on the elbow and ankle were detected by contact counts on the 16th day. Surveys of the thoracic spine with the 2″ collimator were made on days 1, 198, and 285. Also counts on the fifth and eighth vertebrae, and at other positions, were taken on days 2, 3, 34, and 250. Automatic scans with the focusing collimator were made on the ankles on day 16, on the elbows on day 200, and on the spine on days 9, 14, 106, 107, 111, and 112. The background with the patient present was 96 counts per minute. The scan on the 107th day was most detailed with a spacing of only 3/16″ and a total counting time on each point of 50 seconds. The

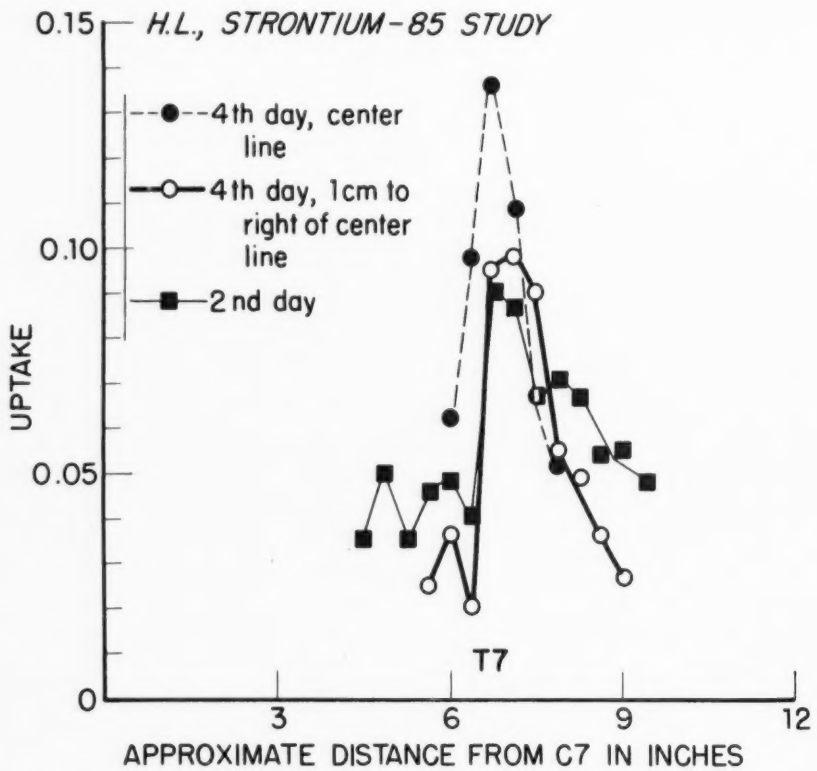

Fig. 5. Results of focusing collimator scans over the spine of H.L. Uptakes are expressed in per cent of the administered dose as measured with the 1″ collimator geometry.

number of counts accumulated in this time ranged from 282 to 470, and consequently the standard error varied from 6 to 9 per cent of the net count rates.

A calibration of the counter was done by counting an aliquot of the injection solution before and after the patient measurements in an easily reproducible geometry. It was done with the 1″ collimator for measurements obtained with this or the focusing collimator, and with the 2″ collimator when the latter was used for the measurements. The standard deviation was less than 1 per cent. The total number of counts in the injected dose was calculated and the uptakes expressed as percentage of the dose. No attempt was made to correct for the geometrical conditions or for absorption. Expressed in this way, uptakes obtained with a specific collimator over a particular site in different patients can be intercompared, although one has to keep in mind that variation will be introduced by differences in size and shape of patients and by differences in excretion.

All counting was done with a gamma ray spectrometer using an 8 per cent channel over the 1.3 mev peak of Ca-47 and a 20 per cent channel over the 0.5 mev Sr-85 peak.

RESULTS

All of the six patients in these studies had breast carcinoma and the usual radiographic studies of the bones had not revealed bone metastases. The results of the spine surveys will be presented first and then the other scans which also illustrate some types of diagnostic information that can be obtained with Ca-47 and Sr-85. The procedure followed in most of these studies was first to make

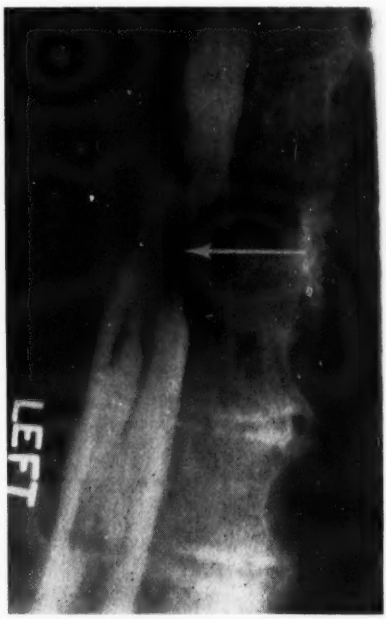

Fig. 6. Myelogram of patient H.L. Arrow marks a compression at the sixth thoracic vertebra.

contact measurements with the 2″ collimator at points along the spine and on other bones of interest. If these measurements indicated the presence of elevated uptake in a bony area, more detailed information about the distribution of activity was obtained from an automatic scan with the focusing collimator.

Four of the patients had had no complaints or clinical findings that indicated bone metastases. One of these, S.J., was studied with Ca-47 and the other three, H.M., S.W., and D.Z., with Sr-85. Patient S.W. had no complaints or metastases while H.M., S.J., and D.Z. had soft tissue involvement. H.M. and S.J. were ambulatory and in good general state of health at the time of study, but D.Z. had been confined to bed for a month as a result of hemiparesis resulting from brain metastasis.

In the three Sr-85 studies, contact measurements with the 2″ collimator were obtained on both the second and third day of each study over many bony

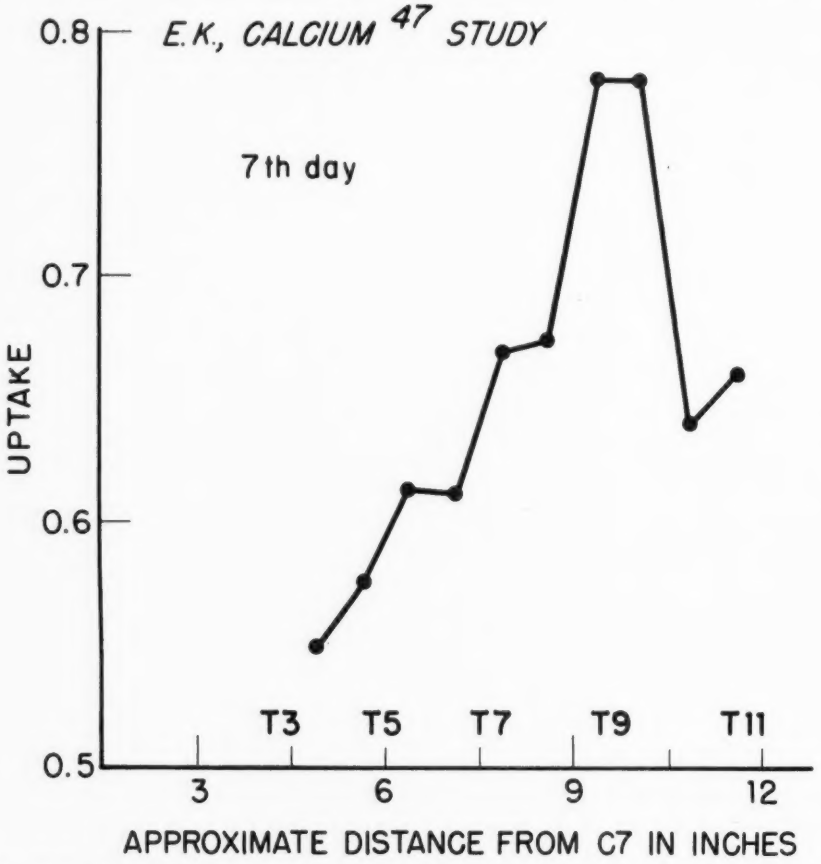

Fig. 7. Results of Ca-47 scan with 1″ cylindrical collimator (E.K.). Uptakes are expressed in percent of the administered dose as measured with the 1″ collimator geometry and as described in the text.

areas. The uptakes over each area had decreased by 5-20 per cent between the two sets of measurements. The ratio of each uptake to that in the tibia was found to vary by less than 10 per cent between the two days. The averages of these ratios are reported in Table II for many of the measuring sites together with the average uptakes in the tibia. A few similar results on S.J. obtained on the third and fourth day of study were reported in a previous report of Ca-47 studies in 30 patients (3). In this case, tibia values averaged 0.36 per cent. The ratios obtained here with Sr-85 are in agreement with those previously reported for the Ca-47 uptake in healthy bones. They also agreed well with each other and were considered normal. Measurements were obtained on both ankles, patellas, tibias, and greater trochanters of each patient, and no significant difference between the right and left sides were found.

TABLE 2

UPTAKES OF SR-85 ON THE SECOND AND THIRD DAYS OF STUDY

Ratio to Tibia Uptake of that in	*H.M.*	*S.W.*	*D.Z.*
Skull	2.7	2.0	3.1
Thoracic Vertebrae	3.0	3.7	4.0
Lumbar Vertebrae	3.2	3.8	3.7
Greater Trochanter	3.6	3.0	—
Patella	3.3	3.1	2.8
Ankle	2.6	2.4	2.6
Uptake in Tibia*	0.29	0.27	0.25

*Uptakes are expressed as per cent of administered dose, as measured with the 2″ collimator geometry.

Measurements along the major part of the spine were obtained on S.J. and H.M. (Fig. 2). It can be seen that the distribution of activity along the spine is similar for both isotopes. For this report, the distribution of activity along the thoracic spine is of particular interest and is illustrated also for S.W. and D.Z. in Figure 3. It appears to be rather uniform although there are slightly higher uptakes between the fifth and ninth vertebrae than above and below these. The ratio of the maximum to the minimum uptakes was calculated for each case and found to be between 1.1 and 1.3.

Patient H.L. had severe pain at the level of the sixth and seventh thoracic vertebrae which radiated towards the right side. On the two days that the patient was counted, several measurements were taken of the Sr-85 uptakes in the painful area as well as at various points above and below on the thoracic spine. One set of measurements is illustrated in Figure 3. The uptakes over the T6 and T7 vertebrae (about 16-18 cm from C7 in Fig. 3) were found to be elevated in all sets of measurements. The fact that the uptakes throughout the spine were smaller than in the other patients could be due to a larger excretion of the tracer and is of little interest here. It is evident that a suspected uptake should be

evaluated in relation to uptakes in other similar bones in the same patient. Therefore, the ratios of uptakes in the T6-T7 area to that in other points of the spine have been calculated and listed in Table 3. An attempt to locate more precisely the area of high Sr-85 uptake was made in the automatic scan shown in Figure 4. Unfortunately, the patient could not remain in a fixed position due to the pain, and the scan was interrupted before the left side of the spine had been surveyed. Inspection of the scan shows a small "hot spot" consisting of seven points with over 80 counts while surrounding areas yielded 30-60 counts in the same time interval.

TABLE 3

RATIO OF THE NET COUNT RATE OVER THE SIXTH OR SEVENTH VERTEBRAE TO THAT OVER OTHER POINTS ON THE SPINE

Patient	*Day of Study*	*Points*	
		4-5 cm above T6-T7	*4-5 cm below T6-T7*
H.M.	2	1.04	1.01
S.W.	3	1.05	0.95
D.Z.	1	0.96	0.96
	2	1.02	1.02
	3	1.01	0.95
H.L.	2	1.38	——
	4	1.51	1.54

The uptakes calculated from two lines of this scan are shown in Fig. 5 together with results obtained two days earlier. It is evident that there is a high uptake peak at T7. These results were taken to indicate the presence of a bone lesion probably small in size, located in the T6-T7 area. Additional evidence was obtained from a myelogram (Fig. 6), showing a small defect in the same place on the right side of the spinal column. A few days after these studies a decompression laminectomy was performed. When the laminae of the 6th and 7th vertebrae were removed, a cuff of tumor about two centimeters long was seen on the right side of the spinal canal. This tumor, which was the cause of the pain, was presumably beginning to produce a bone lesion which was detected on the radiographic films, but was detected with Sr-85 and the HEG scanner.

Uptakes of Ca-47 over several areas of the thoracic spine of patient E.K. are shown in Figure 7. At the time there was no evidence of any metastases with other clinical tests, but she complained about persistent pain in the region of T8. The scan showed a well defined area of high uptake around T8 and was at the

time taken indicate the presence of a bone lesion. Five months later, since the pain still persisted, she was given a second tracer, this time Sr-85. On the first and second days the uptakes over T8 measured on the spine with the 2″ collimator was 1.5 per cent. One representative survey of the thoracic spine is charted in Figure 3. The higest uptakes were here seen between T7 and T10. The ratio of the maximum to the minimum uptakes over the thoracic spine was calculated and found to be 1.4, which was a little larger than in the four patients (S.J., H.M., S.W. and D.Z.) judged to be free of lesions. To elucidate further the distribution of activity in the thoracic spine, many focusing collimator scans were taken with

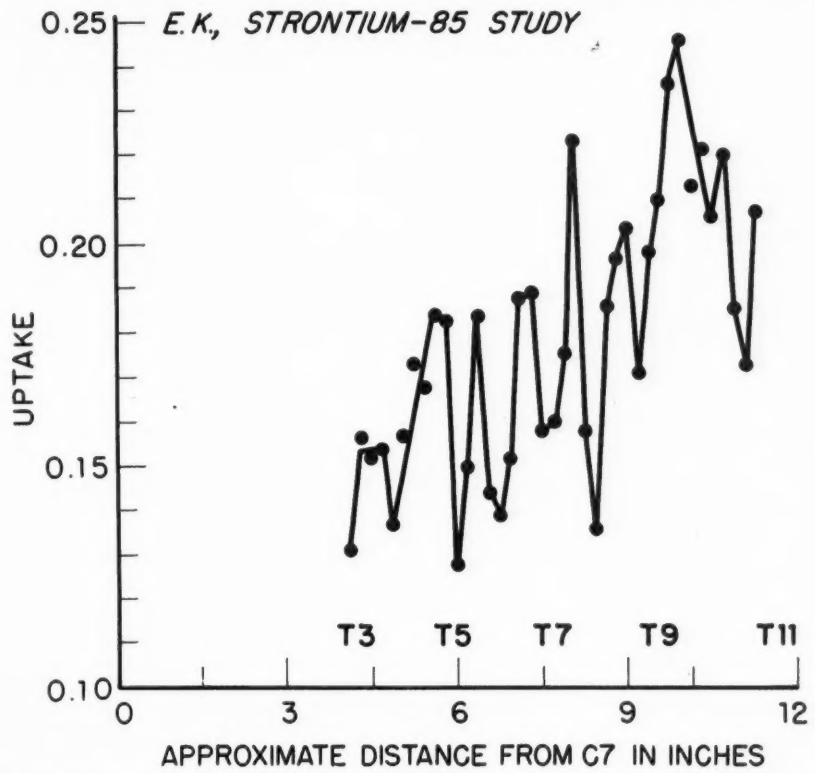

Fig. 8. Results of focusing collimator scans over the thoracic spine on the 107th day of the Sr-85 study. Uptakes are expressed in per cent of the administered dose as measured with the 1″ collimator geometry.

Two successive scans were done over the same area with preset time of 25 seconds and the results have been added. In the total counting time of 50 seconds between 282 and 470 counts were accumulated at each position. The background was 96 counts per minute and had been determined for 5 minutes. This yields a standard deviation of 6-9 per cent of the net count rates. In both scans the eight peaks were observed. The last peak (close to T10) is clearly not statistically significant but has been indicated on the graph because it appeared on both scans together with the other peaks.

essentially identical results (Fig. 8). It was extremely interesting to see that a series of well defined peaks were resolved. The highest peaks were obtained between T7 and T10 and this scan confirmed the impression of the presence of an area of high uptakes covering several vertebrae.

Skeletal surveys and x-rays films of the vertebral column, taken on several occasions, were reported to show only diffuse osteoporotic changes until the first month of the Sr-85 study, when diffuse osteolytic and osteoblastic metastases in

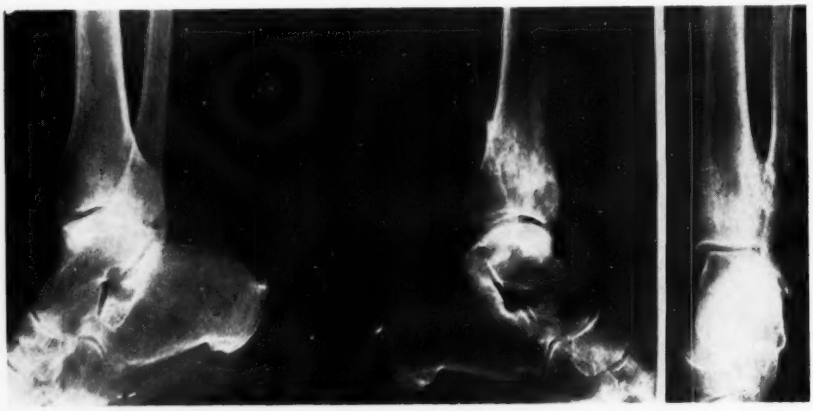

Fig. 9. Radiographs of ankles of E.K. Two views of the left ankle.

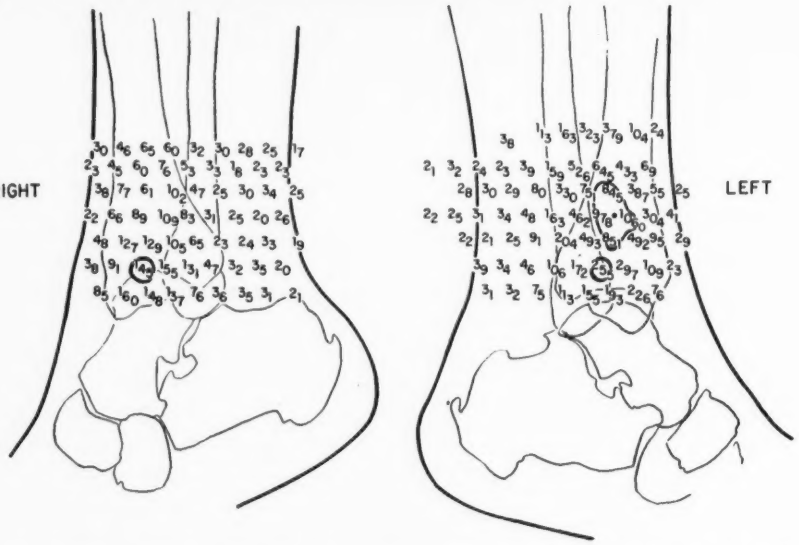

Fig. 10. Focusing collimator scans of ankles superimposed on drawings made from radiographs. Preset time 25 seconds. Background 25 counts in 25 seconds. The small circles indicate the position of each medial malleolus marked during the scan. The larger area marked indicates the "hot spot" as it was outlined immediately after the completion of the scan.

the ribs, skull, pelvis and throughout the spine were diagnosed on radiographs. A bone marrow biopsy revealed the presence of malignant cells. These findings confirmed the interpretation of the Ca-47 scan which had been obtained five months earlier. It is interesting to note that all the scans indicate larger uptakes in the lower part than in the upper part of the thoracic spine while on the x-ray films one can only establish a general metastatic involvement throughout the whole vertebral column.

Some other scans of interest were obtained on this patient E.K. On the 16th day of the Sr-85 study, she complained about pain which had occurred intermittently for a few months in the right elbow and in the left ankle. These, as well as control areas, were scanned and elevated Sr-85 uptakes were detected over the painful spots with the 2″ collimator. The uptake in the left ankle was 5 times that in the right, while the right elbow had more than twice the activity of the left.

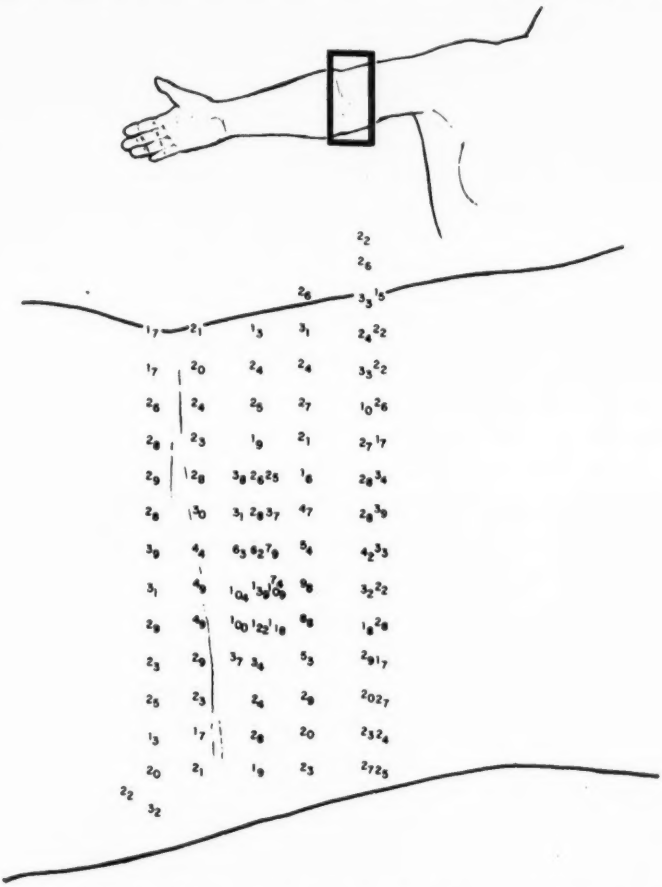

Fig. 11. Scan of elbow (E.K.). Preset time 15 seconds. Background 24 counts per 15 seconds. Spacing at 3/8 inches in the vertical direction.

Radiographs of the ankles were not included in her previous skeletal survey. When these films were obtained (Fig. 9), an osteoblastic lesion surrounded by a sclerotic area and an indication of a small fracture with a displaced bone fragment were seen in the lower end of the left tibia. Figure 10 shows the automatic scans of these ankles obtained with the focusing collimator. It was evident that a rather large lesion existed. The center of it was marked during the scan as shown in the figure and had count rates up to 20 times those in the corresponding points on the other ankle. Inspection of the radiograph showed that the highest count rates corresponded to the denser areas on the film and that sclerotic areas had count rates which were considerably larger than those on the other foot, but smaller than over the avulsed fragment. It is also of some interest to inspect the scan of the right foot. Over soft tissue, counts about background level were obtained, and it was not until the counter was very close to, or over the bone, that uptakes were registered, with the largest values over the medial malleolus and the distal end of the tibia. These scans may serve to illustrate that an area of elevated uptake can be outlined and that differences in uptake within such an area or even an area of healthy bone can be observed and correlated with the radiographs.

Radiographs of the upper arms existed and were considered unremarkable. However, when the elevated uptake in the right elbow had been confirmed repeatedly during the study it was decided to scan the area with the focusing collimator. The result is shown in Figure 11. When the automatic scan was completed the detector was moved back to the area of high count rates and additional readings obtained so as to outline more completely the "hot spot". (This is one example of the convenience of a direct read-out system where results can be inspected during the scanning procedure, as compared to photographic or other methods where the scan is inspected afterwards). In the evaluation of this scan, we then have eight points with counts around 100 outlining a small "hot spot", with an average net count rate of 85 counts per 15 seconds. The net count rates 1″ away from the center of this "hot spot" as well as on the corresponding

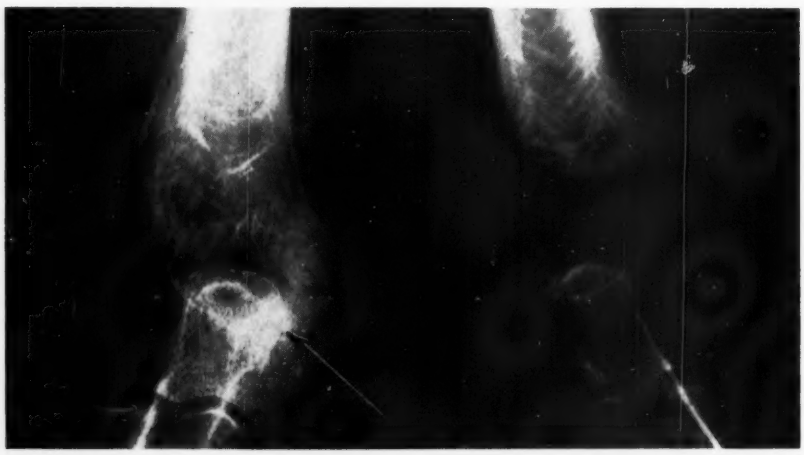

Fig. 12. Radiographs of elbows (E.K.).

place on the left arm are all of the order of 10 per 15 seconds. This convinced us that we had detected another area with elevated calcium uptake in this patient, and the radiographs of the upper arms were re-inspected. A small dense area about 1 cm in diameter was now noted in the medial epicondyle of the right humerus adjament to the olecranon fossa. Figure 12 shows another set of radiographs obtained about the time of the scan, where this area could be seen more clearly. In this case one may say that the abnormal calcium uptake was of direct help in the interpretation of the x-ray film.

DISCUSSION

In our previous work we found that elevated uptakes of Ca-47 in bone lesions including bone metastases could be detected externally. An elevated calcium uptake might occur in combination with normal or abnormal rates of removal of calcium from the same area. The net balance of uptake and loss of calcium will determine the change in mineral content which, if it is large enough, can be visualized on radiographs. Several investigators have studied the radiographic visualization of bone demineralized to varying degrees (6, 7, 8). The results indicated that with conventional techniques a minimum calcium loss of 30 per cent is necessary and possibly up to 50-60 per cent before a decreased density can be detected (9). After disease processes have begun, it may, therefore, take weeks or months before there is enough change in mineral content to be observed on radiographs. In contrast, any process in the skeleton which will cause increased calcium uptake from the body-fluids will result in a simultaneously increased uptake of recently administrated Sr-85 or Ca-47 label. Thus a radioisotope study may give information of the dynamic state of the bone or bone lesions at the time of study.

In order to obtain information about the Ca-47 and Sr-85 uptakes at a limited number of points on the body, a rather simple scintillation probe can be used if it is well shielded. However, considerable additional information can be gained by using the HEG-scanning system as is shown in this study. The relative advantages of the large aperture collimator and the one with a fine resolution such as one tungsten focusing collimator is illustrated by the measurements on the elbow lesion in patient E.K. The detection was first made with the 2″ collimator with which it was found that the right elbow had two to three times the activity of the left. When the focusing collimator was used to outline and define the lesion, the uptake was found to be about nine times that of the uninvolved bone. The differential was, of course, improved when smaller amounts of healthy bone were counted with the lesion. Surveys with the 2″ collimator are faster and also relatively insensitive to the precise positioning of the counter. The count rate is high and represents the activity in a large amount of bone. This is illustrated by the smooth curves of the Ca-47 and Sr-85 distribution along the spine. A similar curve has been presented by Gynning et al. (4) for Sr-85. However, with the focusing collimator, the distribution of activity in one of the patients was found to be very uneven, yielding a series of peaks.

This very detailed information of the activity distribution was gained with a new automatic scanning technique using the quantitative read-out system. In evaluating the results, the statistical accuracy of the counts was taken into

consideration. So, for example, on the ankle scan in Figure 10, the "hot spot" was made up of four points with counts of 800 per 25 seconds. This means that each had less than 4 per cent standard deviation. Therefore, this spot is significantly higher in count rate than the surrounding area with 300-500 counts per 25 seconds, and this in its turn is higher than the count rates over the other ankle. The differences in count rates over various parts of the lesion were thus significant and found to correlate with the variation in density on the radiographs. Another use of the quantitative data is that the count rate at each point of the lesion may be expressed relative to the dose administered, so that the results of repeated tracers can be intercompared. This feature will be particularly useful in research on changes in calcium metabolism in healthy and diseased bone, for example, as a result of therapy.

In this work Ca-47 and Sr-85 have been used interchangeably. It is known that in general the preferential but variable urinary excretion of strontium over calcium leads to a lower retention of strontium isotopes after intravenous injection (10). In our studies it appeared that the retained doses of Sr-85 and Ca-47 were distributed in similar proportions between the various parts of the human skeleton. That the distribution is very similar, at least during the first week after simultaneous injection of Sr-85 and Ca-47 or Ca-45, has been indicated before by external counting of thigh and knee in one patient (5) and by some autopsy analyses (11).

It is of great importance and encouraging that in several instances the initial detection of metastatic lesions in bone with Ca-47 and Sr-85 scanning has been confirmed by other means. In this study the detection of spinal metastases in two patients is described. In one of these Sr-85 uptakes outlined a small lesion which was within a few days confirmed by surgery. In the other case several vertebrae were found to have high Ca-47 uptakes and about five months later metastatic involvement became visible on radiographs. Gynning, et al., reported on one patient where high Sr-85 uptakes preceded by several months radiographic visualization of metastases. Bauer, et al. (5), identified a fine fracture line in a hip possibly of metastatic origin on x-ray films after the position had been established by a Sr-85 study. This case is similar to our detection of a lesion on radiographs of one elbow of patient E.K. after it had been defined by external counting. In all of the above reviewed cases, bone pain was the original complaint which led to the radioisotope studies and it can be concluded that Ca-47 or Sr-85 scanning can be very helpful for clarification of whether a complaint of pain is caused by a bone lesion not yet observed on radiographs. Such information may lead to early treatment and facilitate the management of the patient. That this technique might be developed into a screening method for cancer patients, who do not have any complaints, is an important implication which now will have to be investigated.

SUMMARY

The HEG scanning system, designed specifically for external counting of high energy gamma rays, has been applied towards the diagnosis of bone metastases from breast carcinoma. In this report studies on six patients are described who had been given intravenous injections of either calcium-47 or strontium-85.

In four of these cases there was no evidence of bone metastases and the radioisotope uptakes in a variety of bones were normal. Of particular interest in this work was the distribution of activity along the thoracic spine. With a straight hole collimator in the scanning head, the uptake was found to be fairly constant throughout, although, between the fifth and the ninth vertebrae, uptakes 10-30 per cent larger than above or below were sometimes seen.

Two patients had complaints of pain in the thoracic spine. Elevated uptakes were detected over the painful areas while radiographs were not reported to show bone lesions. The presence of metastases were confirmed in one case by surgery and in the other case after five months by radiographic examination.

The scans of these and other lesions presented in this paper demonstrate that the HEG scanning system with its quantitative read-out has advanced the possibility of detecting and outlining bone lesions and also has made it possible to obtain more precise data on the calcium turnover in the lesions.

The scanning technique and the clinical implications of the findings have been discussed.

ACKNOWLEDGEMENT

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JOURNAL OF NUCLEAR MEDICINE 3:472-479, 1962

Protection from Radiation Induced Lethality by Chemical Mixture and Partial-Body Shielding[1]

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Buffalo and Cincinnati

INTRODUCTION

Mixtures of two radioproductive agents, 5 μM serotonin plus 10 μM 2-aminoethylisothiuronium (AET) or 5 μM serotonin plus 30 μM 2-mercaptoethylamine (MEA) given to CF_1 mice preceding exposure to 1100 r of total-body X-irradiation at this laboratory, were found to give 70 to 80 per cent survival (1). Subsequent work has shown that while mixtures of the above agents offered practically no protection to mice receiving 1400 r, a mixture containing all three agents, 2.5 μM serotonin plus 7.5 μM AET and 30 μM MEA, afforded mice 50 to 60 per cent protection (2).

Maisin *et al* reported that a small amount of protection against the lethal effect of radiation was obtained by the use of combined chemical (MEA) and lead shielding of the hepatic region in rats, and improved protection was achieved by the use of MEA and lead shielding of bone marrow (3). Again investigators at this laboratory demonstrated that partial-body shielding by lead grids gave beneficial effects on the survival and recovery of total-body irradiated animals (4). However, shielding by the use of grids failed to produce any 30-day survivors at 1200 r midline tissue dose(4).

The present study was undertaken to determine the degree of protection afforded by the combined use of chemicals and grid shielding in mice exposed to X-irradiation at supra-lethal dose levels.

EXPERIMENTAL

Adult female CF_1 mice weighing between 21 and 25 grams were used. The mice were housed in an air-conditioned room nine to each jar and were given Purina laboratory chow and water *ad libitum*. They were observed for at least

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two weeks prior to their use. Mice selected for the studies were divided at random into different experimental groups from a single shipment of mice so that their age and weight would be comparable.

The grid was constructed from lead sheets 3.2 mm thick. Measurements showed that this thickness of lead transmitted only two per cent of the incident radiation dose. The apertures of the grid were 0.19 cm in diameter and were distributed as uniformly as possible over a circular area of 189 sq. cm. with approximately 16 apertures per sq. cm. The X-irradiations were performed with a General Electric Maxitron Unit operated at 200 kvp, 30 ma, 0.1 mm Al equivalent inherent filtration, half-value layer of 4.0 mm Al, 44 cm source to mid-animal distance, and a dose rate of 150 r/min. Figure 1 shows the arrangement for exposing the mice to the X-radiation through grids. The open area of the grid was originally calculated to be 45.3 per cent. However, the distances between the centers of the grid apertures were not made precisely to the degree of no error. The true measured open area of the grid was found to be 41.6 per cent. This value was obtained by placing the ionization chamber in one of the paraffin phantoms at

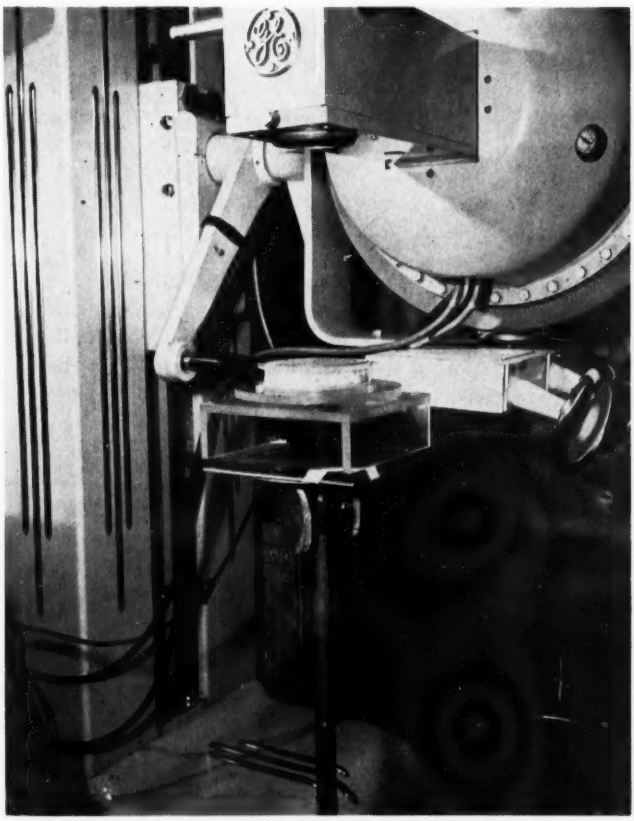

Fig. 1. Experimental arrangement for exposing mice through grids to X-radiation.

TABLE 1

PROTECTION BY CHEMICAL MIXTURE AND PARTIAL-BODY GRID SHIELDING FROM RADIATION-INDUCED LETHALITY

Treatment	*Mid-Tissue X-ray Without Grid*	*Dose (r) With Grid*	*No. of Mice Irradiated*	*No. of Mice Survived*	*% Survival 30-Day*
None	1400	—	18	0	0
	1700	—	9	0	0
	2000	—	9	0	0
Partial-Body	(3365)	1400	18	0	0
Grid Shielding	(4087)	1700	18	0	0
	(4808)	2000	18	0	0
Chemical Mixture	1400	—	33	26	79
	1700	—	35	16	46
	2000	—	32	7	22
	2300	—	26	0	0
Chemical Mixture	(3365)	1400	54	53	98
Plus Grid Shielding	(4087)	1700	54	47	87
	(4808)	2000	54	40	74
	(5529)	2300	23	4	18

the approximate location of the mouse midline in the lucite cage. The grid was placed on the cage cover which was kept stationary during the dose measurement. The remainder of the cage (including paraffin phantoms and ionization chamber) was rotated during the radiation exposure. Since the mice exposed through the grids received only 41.6 per cent of the dose incident to the grid, compensation for the lower dose to the grid-shielded mice was made by increasing the exposure times to subject the shielded mice to the corresponding total midline tissue dose of the non-shielded mice.

The procedure for intraperitoneal injection was conducted aseptically. Fifteen minutes prior to radiation exposure the mice to be shielded were anesthetized with 1.0 mg of pentobarbital intraperitoneally. Either with or without the chemical mixture after they became immobilized, they were placed carefully nine at a time in prone position in a shallow lucite cage. The grid was placed directly on top of the cage in close proximity to the dorsal surface of the immobilized mice. To ensure uniform irradiation of all mice, the cage was put on a rotating table during the exposures. It should be emphasized that differing from the condition of measuring the open area of the grid, here the grid was allowed to rotate with the cage. Thus, the open areas of the grid were always in the same fixed position relative to the immobilized body of the mice during irradiation.

Since preliminary experiments indicated that there was no difference in re-

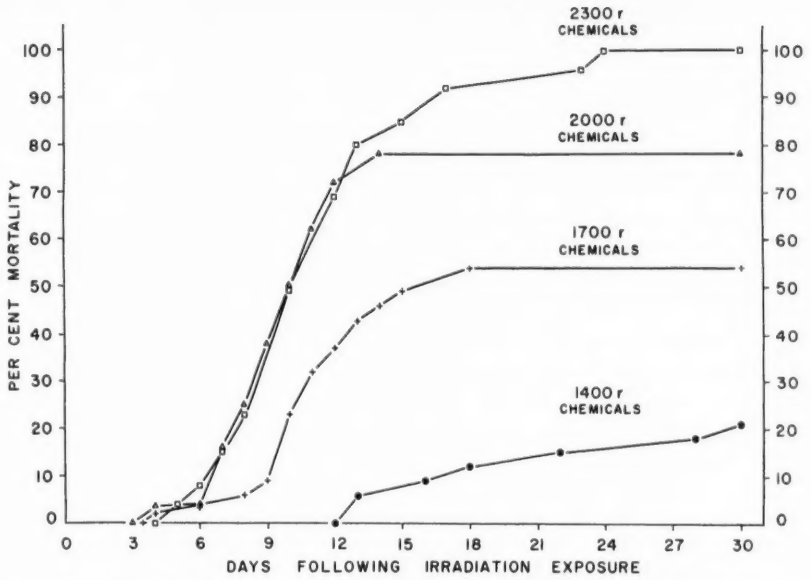

Fig. 2. Mortality of chemically treated mice exposed to supra-lethal doses of total-body X-irradiaton.

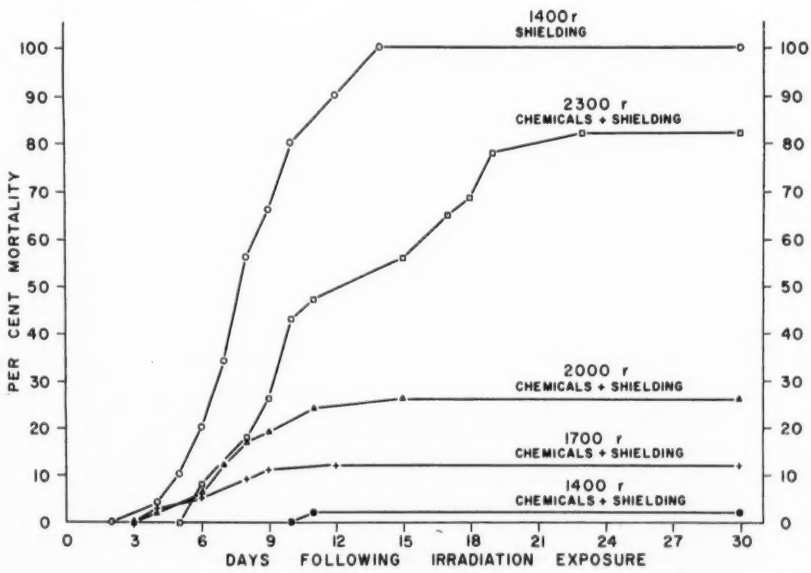

Fig. 3. Protection from radiation induced lethality by the combined chemical treatment and grid shielding.

sponse to neutralized or unneutralized solutions, the chemical mixtures was freshly prepared in sterile solution without neutralization. The radio-protective mixture consisting of 2.5 μM serotonin (50.6 mg/kg) plus 7.5 μM AET (105.4 mg/kg) and 30 μM MEA (171 mg/kg) of their salts per mouse was given intraperitoneally to the immobilized mice about 10 minutes prior to radiation exposure. The mortality of mice following exposure was recorded every 24 hours for 30 days.

RESULTS

LD_{100} for CF_1 mice receiving 1.0 mg of pentobarbital intraperitoneally prior to radiation exposure was found to be 900 r. The LD_{50} for untreated mice is 570 r (1). The LD_{50} for pentobarbital treated and grid shielded mice is 1000 r (4).

The results of this study for control and protected mice exposed to supra-lethal doses of total-body irradiation are shown in Table 1. All 54 mice with or without partial-body grid shielding irradiated at supra-lethal doses of 1700 or 2000 r, died within five days following exposure. Both groups of 18 mice without partial body shielding and 18 mice with partial-body shielding died within 6 and 14 days respectively following exposure to 1400 r.

When groups of 126 mice without grid shielding were given pre-irradiation administration of radioprotective chemical mixture (2.5 μM serotonin plus 7.5 μM AET and 30 μM MEA per mouse) and were subjected to midline tissue doses of 1400, 1700, 2000, or 2300 r, survivals of 79, 46, 21, and 0 per cent, respectively were observed (Figure 2). When a group of 185 mice with both grid shielding and pre-radiation chemical mixture were irradiated with the same mid-tissue doses of 1400, 1700, 2000 or 2300 r, survivals were increased to 98, 87, 74 and 18 per cent, respectively (Figure 3).

Two per cent of the mice treated with pentobarbital and the chemical mixture died within 24 hours. These mortalities are attributable to drug-induced toxicity and therefore not included.

DISCUSSION

Protection against radiation-induced lethality may be achieved by employing one or a combination of several procedures, among which are (1) pre-radiation administration of radio-protective chemical agents, (2) post-radiation therapy with cellular material, primarily bone marrow, (3) total or partial-body shielding during the radiation exposure, and (4) subjecting the animal to hypoxic or anoxic condition at the time of irradiation.

It has been demonstrated that radioprotective agents when used individually afford some protection to rodents in the lethal dose range. Improved protection in terms of increased 30-day survival and extension to supra-lethal doses can be obtained by the administration of mixtures of known radioprotective agents (1,5). However, even with the most effective chemical mixture (2.5 μM serotonin plus 7.5 μM AET and 30 μM MEA), protection of mice at high doses of radiation (2000 r or above) is limited.

Partial-body shielding by placing solid lead sheets over selected radiosensitive areas of the animal body is known to afford protection against radiation. In some instances, organs have been exteriorized and subsequently shielded with

lead during the radiation exposure. Shielding by the use of grids affords a radiation-dose distribution such that portions of body tissues are irradiated but adjacent areas are relatively less exposed. This partial-body shielding procedure has been shown to offer some protection to rodents exposed to mid-tissue lethal doses of 900 r and not over 1200 r.

The limitation of these protective procedures may be alleviated by providing both pre-radiation chemical treatment and partial-body shielding to the animals to be irradiated. Maisin *et al* noted the beneficial effect of pre-radiation administration of MEA and solid lead shielding of selected areas of the body. Among the partially shielded portions of the body greater protection to those animals that received shielding of the bone marrow during irradiation was observed. Thus, they believed that the amount of protection was dependent on the site of the body that was shielded.

The results of the present study indicate that pre-radiation administration

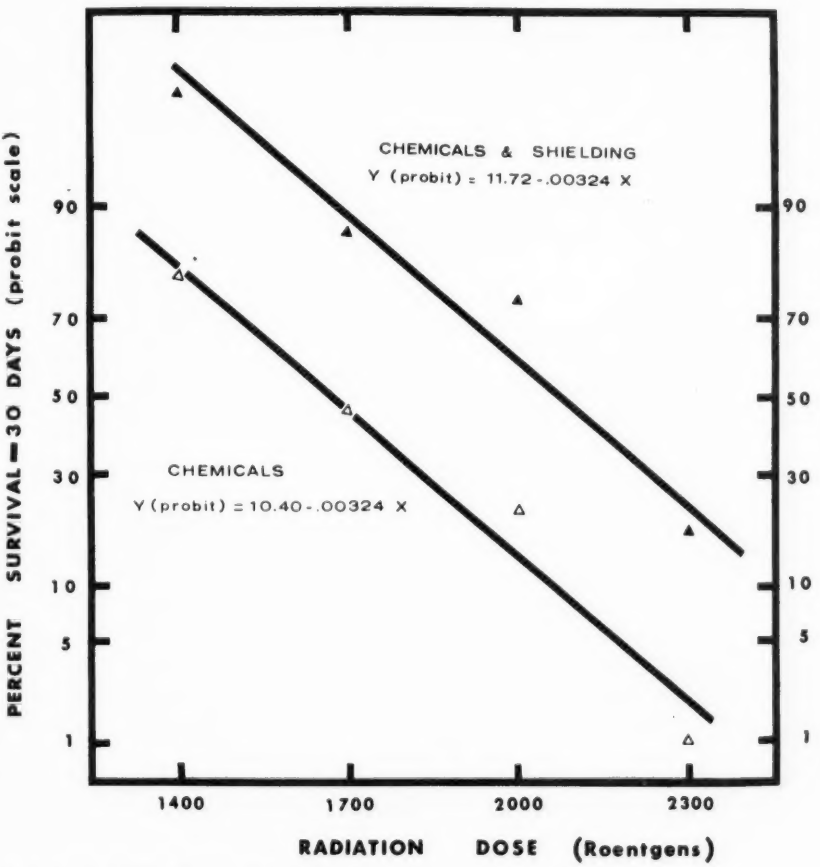

Fig. 4. Dose survival curves on probit scale.

of chemical mixture containing 2.5 μM serotonin, 7.5 μM AET, and 30 μM MEA provided excellent protection to mice at 1400 r (79 per cent survival 30-day). Slightly less than half of the mice were protected from the lethal effect of radiation by this chemical mixture at 1700 r. However, the combination of pre-radiation chemical treatment and partial-body shielding by the use of grids protected 98 per cent of the animals at 1400 r. This combined protective effect became increasingly significant in mice exposed to higher doses of radiation. The greatest beneficial effect of the combined chemical treatment and partial-body shielding was observed in mice irradiated at 2000 r. While only 22 per cent survival was found in the chemically treated mice at this dose, 74 per cent of the mice with combined protection remained alive. Since partial-body shielding by grids is known to provide no protection to mice exposed to doses above 1200 r, this additional 52 per cent survival could be attributable to the beneficially additive effect of the two types of protection.

The precise meaning of dose reduction is not entirely clear. The following data is presented so that the dose reduction factors can be calculated and compared:

(a) The LD_{50} for untreated CF_1 mice is 570 r (1).
(b) The LD_{50} for the grid shielded mice (receiving 1.0 mg pentobarbital) is 1000 r (4).

When the percentage survival curves for the chemically treated and chemicals plus shielding were plotted as probit against the linear radiation dose as shown in Figure 4, it was found that the slopes of the two curves were not significantly different so that a common slope was taken ($-.00324$).

(c) By assuming probit $Y = 5.00$, the LD_{50} for chemicals is about 1667 r (Y (probit) $= 10.40 - .00324\,X$).
(d) Similarly, the LD_{50} for chemicals plus shielding is approximately 2074 r (Y (probit) $= 11.72 - .00324\,X$).

The dose reduction factor of 2.9 (1667/570) or of 2.1 (2074/1000) is obtained for the effect of the chemical mixture. A dose reduction factor of 1.24 (2074/1667) or 1.75 (1000/570) is obtained for the effect of shielding. The highest dose reduction factor is 3.6 (2074/570) or the combined effect of chemicals plus shielding.

Comparison between (a) the LD_{50} for untreated mice (570 r) and (b) the shielded mice (1000 r) reveals a difference of 430 r. Comparison between (c) the LD_{50} for chemicals (1667 r) and (d) chemicals plus shielding (2074 r) shows a difference of about 407 r. The difference of 430 and 407 r is small; thus the enhancement of grid shielding is additive when used with chemical protection.

SUMMARY

Partial-body shielding by the use of lead grids offered some protection to mice exposed to mid-tissue doses of 900 r but not over 1200 r (dose reduction factor between 1.24 and 1.75). Pre-radiation administration of chemical mixture

containing 2.5 μM serotonin, 7.5 μM AET, and 30 μM MEA provided 79, 46, 21, and 0 per cent survivals in mice exposed to 1400, 1700, or 2300 r, respectively (dose reduction factor between 2.1 and 2.9). However, the combination of pre-radiation chemical treatment and partial-body shielding increased the survival of mice irradiated with the same mid-tissue doses of 1400, 1700, 2000 or 2300 r to 98, 87, 74 and 18 per cent, respectively (dose reduction factor of 3.6). This increased survival could be attributable to the beneficially additive effect of the two types of protection.

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MEETING NOTICE

8th HAHNEMANN SYMPOSIUM

Title: Medical Considerations in the Surgical Patient

Sponsored by: Hahnemann Medical College and Hospital
230 North Broad Street, Philadelphia 2, Pa.

Date of Meeting: December 12 to 14, 1962.

Location of Meeting: Sheraton Hotel
1725 Pennsylvania Blvd., Philadelphia 3, Pa.

Purpose: To consider the major medical problems which the physician encounters in the surgical patient. The program is divided into the following subsections:

1. Evaluation and preparation of patients with difficult cardiovascular problems requiring surgery
2. Therapy of cardiovascular-pulmonary problems in the postoperative period. Special emphasis on fluid and electrolyte problems, cardiac surgery problems and the diagnosis and management of shock
3. The evaluation of endocrine problems in the pre- and postoperative period
4. Evaluation and management of gastrointestinal disorders in the pre- and postoperative period

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JOURNAL OF NUCLEAR MEDICINE 3:480-485, 1962

Renal Blood Flow Measurement From The Disappearance of Intravenously Injected Hippuran^{I-131} [1,2]

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INTRODUCTION

An accurate method of estimating renal blood flow which avoids both bladder catheterization and dependence upon relatively large urine volumes would be a useful tool in clinical investigation. Renal blood flow can be estimated by measuring the disappearance of a suitable material from the blood following a single intravenous injection. The basic requirements are that the material used be cleared only by the kidneys, that it reach its volume of distribution quickly, and that it leave this volume easily so that the change in concentration observed in the blood will be representative of the change in concentration in the entire apparent volume of dilution of the tracer. This method was suggested several years ago (1, 2, 3) but cleared substances were difficult to measure accurately in low concentrations and the method was generally discarded. In this study we show that the use of orthoiodohippurate (I^{131}) (Hipputope^{R}, Squibb) satisfies the conditions for a method of measurement which makes this a useful, accurate technic for measuring renal blood flow. The radioactive tracer also makes possible simultaneous renograms by external counting.

METHODS

I^{131}labeled hippuran was injected intravenously from a 1.0 cc. syringe in amounts varying from 0.2 to 1.0 microcurie per kg of body weight. This produces a whole blood concentration of hippuran of approximately 3 micrograms per 100 mls initially and less than 1 microgram per 100 mls. after 10 minutes, that is 1/3000 of the concentration of PAH usually used in the classical PAH-clearance

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[3]Part of this work was performed in accordance with the requirements for the degree of Doctor of Medicine at Western Reserve University by Mr. Gott.

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ERBF measurement. External counting was achieved by scintillation counting with collimation previously described in measuring cardiac output (4). When continuous strip-chart recording from the external counters was used, the marker pen attachment recorded permanently all times of injection, drawing of blood samples, etc. When the study was performed at the bedside or outside of this laboratory, the times were recorded from a stop watch. Serial venous or arterial blood samples were drawn and 3.0 ml of whole blood aliquots of these samples were counted in a well-counter. For some studies, urine was collected by voiding or by catheterization.

In the series with simultaneous measurement of renal flow by the para-aminohippurate clearance technique, the subjects were studied at the Cleveland Metropolitan General Hospital by Dr. Elmerice Traks and associates in the laboratory of Dr. Salvatore Sancetta. Results were then compared with their measurements and expressed as per cent deviation from the PAH values.

In some patients external counters over the kidney regions recorded a continuous curve of activity on strip-chart recorders. For precordial counting our previous technique (4) was used.

RESULTS

Characteristics of ortho-iodohippurate (I^{131}):

A. Renal Clearance.

Non-radioactive ortho-iodohippuric acid, hippuran, is considered to be

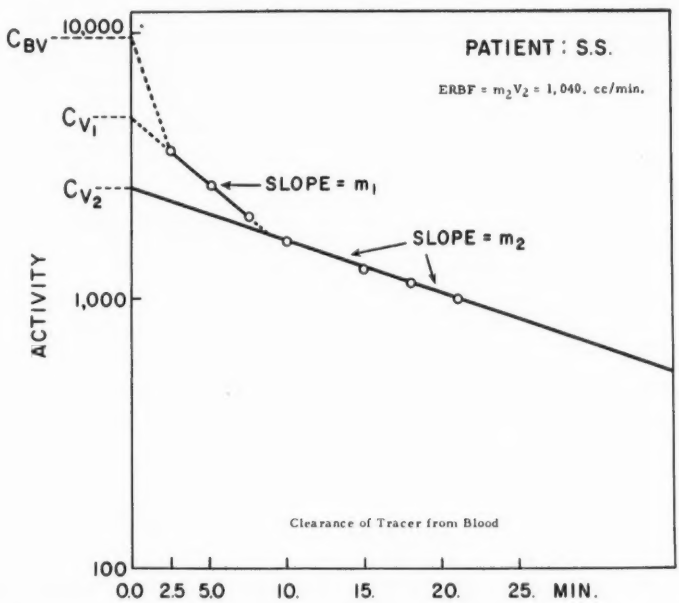

Fig. 1. Concentration of Hipputope in whole blood plotted vs. time on semi-log paper for determination of ERBF.

cleared by renal action alone (5) and the I^{131}-labeled hippuran also has been found to be cleared only by the kidneys (6, 7). External counting in this laboratory has revealed no other area of increased concentration.

B. Blood concentration vs. time curve features.

In addition to sole excretion by the kidney, a prerequisite for its use in this method is that this tracer reach its volume of distribution within the body quickly. The blood concentration after injection was observed both by counting serial blood samples and by external counting of the blood pool within the heart with a counter placed over the precordium. The concentration plotted versus time is illustrated in Figure 1. The rapid fall observed during the first 3 or 4 minutes indicates a dilution due to mixing and rapid diffusion across the capillary membrane surfaces. This rapid rate of disappearance of labeled hippuran from the blood during this interval has been calculated to be equivalent in amount of clearance to two blood volumes in 2.5 minutes. This greatly exceeds clearances by all possible organ systems, and must be due to mixing and a rapid diffusion to extra vascular spaces.

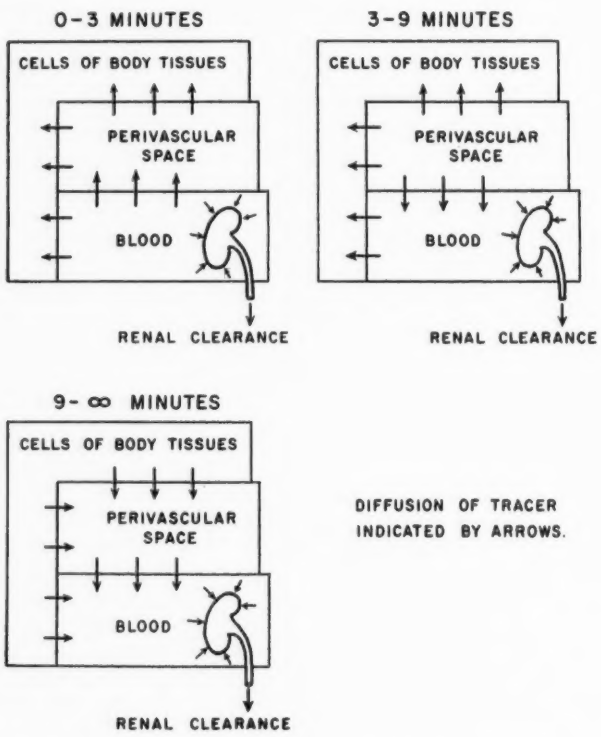

Fig. 2. Hypothesis of tracer diffusion following a single injection.

In an analysis of curves obtained from more than 50 patients, in addition to the early fast 0 to 4 minute slope, two subsequent rates of fall in concentration were observed. Approximately 3 or 4 minutes after injection, the concentration curve merges into a different and less rapid slope of disappearance. This new rate was consistently maintained to approximately 9 minutes after injection. If this 3 to 9 minute disappearance slope is extrapolated back to zero time, a dilution volume close to 16 per cent of the body weight in normal subjects and 16 per cent of the estimated normal body weight of obese and edematous subjects was found consistently.

In patients with edema we have placed Southy tubes into the edematous subcutaneous tissue and found virtually no appearance of the tracer in the edema fluid being drained during a 30-minute period following injection. Because of this and the relatively brief time of diffusion, it is postulated that this disappearance rate is the result of diffusion from the blood into a space or spaces in close proximity to the vascular bed. This extra dilution space reached in 3 minutes we have called a "perivascular space" so as not to confuse it with total extracellular fluid space (Figure 2).

At approximately 10 minutes, the declination of the concentration curve again appears to change to a slower rate. After this time there consistently is seen a monophasic logarithmic decline with a calculated half time rate of fall ranging between 12 and 24 minutes in over 50 curves examined. Ten minutes or more after injection, the falling curve of concentration is assumed to be due to renal clearance alone.

Figure 1 presents a typical curve consisting of three discrete slopes in three discrete time intervals; this is the curve consistently obtained in over fifty studies. The third slope may extend beyond the 25-minute point, but preliminary results indicate some departure from the previous clearance, possibly due to low carrier effects. In virtually all our studies the third slope was determined by four points obtained starting 10 to 12 minutes following injection. As the samples were drawn at 3-minute intervals the last point used was usually 22 to 24 minutes after injection but occasionally it was drawn more than one-half hour after injection.

Extrapolation of this 10 to 25 minute phase of the declining curve to 0 time allows the calculation of the volume from which the tracer is being cleared during this time. Calculated volumes have ranged from 14 per cent to 30 per cent of body weight with an average of 27 per cent. This variation is in contrast to the volumes found during the 4-10 minute region of the curve which was quite regularly 16 per cent of true body weight.

Thus by using this 10-25 minute phase of the curve, which we have assumed is essentially due to renal clearance alone, a mathematical expression for clearances easily derived from standard formulas could be applied, i.e.:

Renal Clearance = mV, where m = slope of concentration curve, and V = volume from which tracer is being cleared.

Renal clearances calculated by this formula using the 10-25 minute interval of the curves gave excellent correlation with effective renal blood flow simultaneously measured by the classical technic of constant infusion of para-aminohippurate and urine collection. Table I gives these results. There was good agreement in all six experiments with renal flows ranging from 412 cc/min to 1179 cc/min, with an average difference of ±6.9 per cent and a 95 per cent confidence level of +9.9 per cent to −7.6 per cent.

DISCUSSION

The theory of the application of this method is dependent entirely on obtaining an early equilibrium of tracer material and a subsequent clearance by the kidneys alone. Analysis of our curves shows that a volume indicative of such an equilibrium has been reached within the first 9 to 12 minutes after injection of the tracer. The subsequent disappearance from this volume proceeds as a semi logarithmic function with clearance attributable to renal function alone. Empirical correlation with the conventional PAH clearance method over a wide range of renal flows provides the primary basis for these assumptions.

Although the boundaries of this theoretical space are undefined, this does not affect the basic hypothesis upon which the method is based. After approximately ten minutes, the diffusion of the material into the hippuran space appears to approach equilibrium. The slope of this early curve to equilibrium is steep, but the subsequent removal of tracer material by renal clearance exhibits a slower rate of removal than the earlier diffusion rate into the hippuran space. This allows the blood samples to reflect concentration of tracer, not only in the blood, but also of the concentration in the hippuran space itself.

Extrapolation to zero of the 3 to 10 minute diffusion curve gave values which were consistently in the range of 16 per cent of body weight. This value is similar to those obtained with Inulin (8) which requires a much longer period for equilibrium, again suggesting that hippuran diffuses at a very rapid rate.

The technique of this method is uncomplicated and does not require initial loading, constant infusions, or careful urine collections. Although the renal extraction ratio of hippuran has been found to be similar to that of PAH (5), we have not yet obtained extraction ratios of this material in normal patients or in abnormal states.

We have recorded many radioactive renograms by external counting over each kidney. The measurement of renal blood flow was measured by the above method and external renograms were made from the same injection. The additional quantitative estimation of effective renal blood flow may be used with the interpretation of the renograms to better estimate individual renal blood flow.

The low dosage of tracer used and its subsequent rapid removal from the body affects a very low radiation exposure to the subject and allows repeating of the test in the same subject at relatively frequent intervals. (Figures 3 and 4).

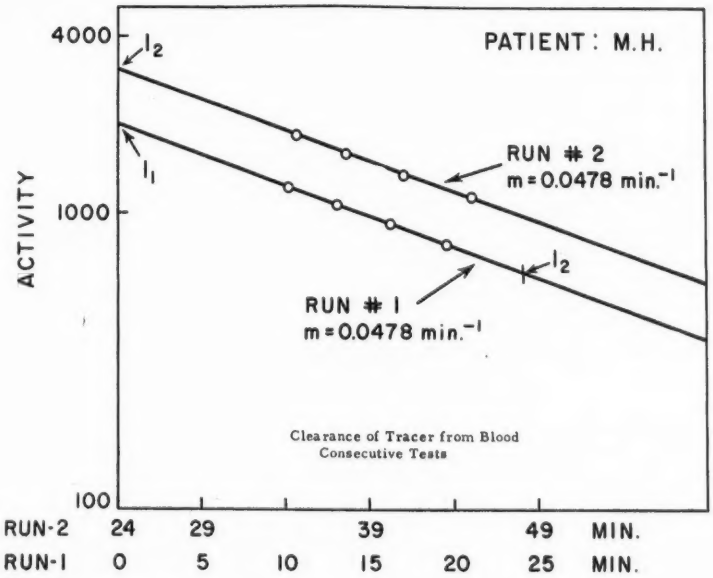

Fig. 3. Consecutive studies in same subject.

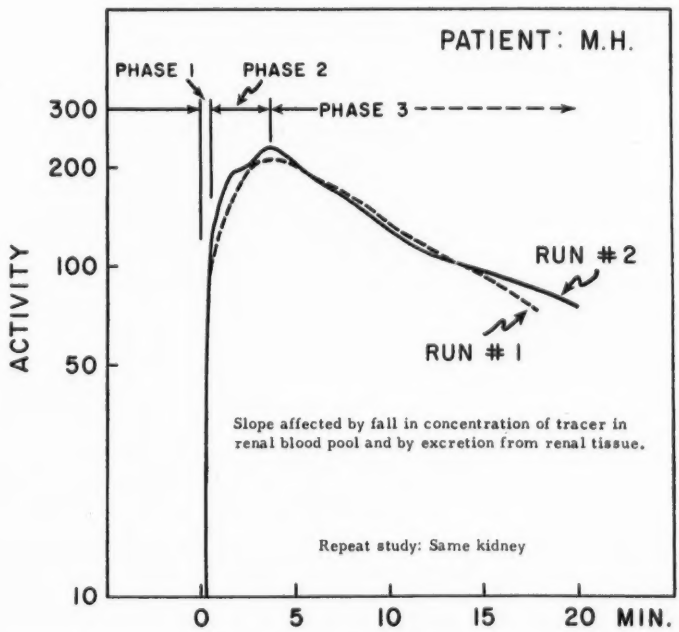

Fig. 4. External renograms obtained in consecutive studies on same subject.

SUMMARY

A fast, simple, and accurate method of determination of total effective renal blood flow without collection of urine is presented.

The technic used is described.

The advantages of the method are discussed.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the cheerful assistance of Mrs. Jeanette Burgermeister Wilson, research assistant, and Dr. Elmerice Traks of the Cleveland General Hospital.

TABLE I.

EFFECTIVE RENAL BLOOD FLOW

Date	*Single Injection of Hippulope Clearance*	*Constant Infusion of PAH and Urine Analysis*	*Percentage Difference*
9/ 2/60	880. cc./min.	965. cc./min.	−8.7%
9/30/60	690.	640.	+7.8%
10/ 7/60	1,105.	1,179.	−6.3%
10/14/60	865.	800.	+8.0%
10/21/60	402.	412.	−2.4%
2/ 4/61	965.	890.	+8.4%
TOTALS:	4,907.	4,886.	41.6 (6)

95% confidence limit = +9.8% to −7.6%. Average difference = ±6.9%.

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The International Atomic Energy Agency's Work in the Field of Nuclear Medicine[1]

by

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The International Atomic Energy Agency came into being late in 1957 as one of the scientific and technical organizations of the "family" of the United Nations. Its Headquarters are in Vienna, Austria, and there are at present 77 Member States, including all major and medium atomic powers and the majority of the so-called less developed countries. The Secretariat comprises about 600 people of whom some 150 are scientists or otherwise technically qualified professional officers. At present, 43 nations are represented on the staff.

The idea of setting up an international "Atoms for Peace" organization was conceived by President Eisenhower in 1953, and at that time, its first and foremost task was thought to be to act as an international "exchange bank" for nuclear fuel materials. It took four years for the Agency to come into being. In the intervening period the power and fuel situation had changed considerably: the expected acute shortage of conventional fuels had not materialized and conventional power costs had gone down; uranium had ceased to be a monopoly material in short supply; finally, power reactors had shown technological snags and proved temporarily less economical than had been anticipated. Consequently, the role of the Agency has gradually changed to that of a major international supplier of information, training and technical assistance for all peaceful applications of atomic energy. Because of their practical importance, the medical uses of atomic energy soon gained a prominent part in the Agency's activities. The present report deals with the Agency's work in this field—what has been achieved in the past three years and what it is hoped to accomplish in the near future. Related programmes of the Agency's work such as those concerned with the medical aspects of health physics, radiation protection, radiation effects and radiobiology, are not considered.

ACTIVITIES OF THE AGENCY

The various Agency activities (1) may conveniently be divided into seven

[1]Based on a talk given by one of the authors (H.V.), December 1961 at the Department of Biophysics and Nuclear Medicine, University of California, Medical Center, Los Angeles, U.S.A.

categories. The first three are specifically concerned with training; the others are of interest both to advanced and less advanced centres:

1. *Fellowships* (2). This is the first step in the training programme. A young scientist, usually from a less developed country, is sent to a more advanced country, normally for one year, to receive basic training in the use of radioisotopes or any other peaceful application of atomic energy;

2. *Training Courses.* Sometimes, fellows are brought together in groups of 20 to receive training in the form of a two-months' course organized by the Agency in a fairly advanced institution. Such training courses are given either on an international or a regional basis;

3. *Technical Assistance* (3). The second basic training method is the opposite of the fellowship programme. Here, an expert from a more advanced country is sent to an institute in a less developed country. Usually the local people with whom he works have already received a basic training abroad and are now taught more sophisticated techniques. When necessary, the expert is provided with a limited amount of equipment which remains in the country after his departure;

4. *Research Contracts.* Once an institute stands, so to speak, on its own feet and has an interesting research project on hand it may be awarded a research contract under the terms of which salaries, supplies and equipment necessary for the successful execution of the project are provided by the Agency. A special type of research contract may also be awarded to an advanced institute to facilitate work of special interest to the Agency;

5. *Conferences and Symposia.* The Agency organizes scientific meetings both on subjects of general interest with a fairly large attendance and on highly specialized topics with not more than 50 to 100 participants. These meetings fulfill a triple function: they provide an opportunity for experts to meet and exchange information; they further the training of the less advanced participants; and, through the publication of the conference proceedings, they facilitate the rapid dissemination of information in a convenient form;

6. *Special Projects and Studies.* While most of the aforementioned activities are carried out in institutions located in Member States, a considerable amount of scientific work is also done at the Agency's Headquarters in Vienna, mainly by the Agency's own scientific staff. An example is the elaboration of standardized methods or of internationally acceptable recommendations in respect of health and safety measures. Not infrequently, the advice of outside experts is sought and special panels are called to Vienna for this purpose;

7. *Laboratory Work.* The Agency is the only organization within the framework of the United Nations which has its own laboratory. Right now this laboratory is comparatively small—not more than 40 people are working in it—but there is reason to hope that it will grow. So far, nuclear medicine has no place in the laboratory's work but this will soon change.

The means by which these various activities are used to further the applications of radioisotopes in medicine will be discussed in the sections which follow.

THE FELLOWSHIP PROGRAMME

It is interesting but perhaps not surprising to note that the medical field is the largest within the fellowship programme: nearly 200 fellowships have so far been awarded to physicians and hospital physicists from the less advanced countries, the majority for training in diagnostic applications of radioisotopes rather than in therapy. The first fellowship which the Agency awarded, was in nuclear medicine. It is also not surprising to see that the majority of fellows have gone to the United States for training. The fact that most of the U.S. laboratories are well ahead in nuclear medicine ensures, of course, that these fellows receive training in the newest techniques and return home fully briefed on the latest developments and most promising research lines. However, there is also a definite disadvantage which is not easy to avoid. The laboratory to which the fellow has been sent, may in fact be *too* advanced: it is likely to be spacious if not palatial, may have a considerable amount of automatic counting and recording equipment, many large crystals and precision spectrometers and, above all, too efficient auxiliary services. As a result, when the trainee returns home he often finds himself helpless vis-à-vis the common small but nonetheless difficult problems which so often arise in the so-called underdeveloped countries but which he has never encountered in the host country. Once, an Agency mission met a radiologist who had spent five years at an American university and had even been awarded a degree in nuclear medicine but had never cleaned a radioactive syringe himself because this had always been done for him by a laboratory technician. In another country, equipment had been lying idle for more than two years because the mains cable had broken and the man in charge had never been taught how to repair a broken cable. He had only learned which number to dial to get a new cable delivered next morning!

Even more serious may be the question as to the type of problem the trainee should be put to and the isotope techniques he should learn. Another Agency mission once met a physician who had spent two years in a laboratory in the United States where he had done nothing else than use C-14 to study glucose metabolism of the isolated heart muscle of the rat. When he returned to the hospital in his own country, there was no C-14 counting equipment, no Warburg apparatus, and the only rats were those in the streets. The man never took up isotope work again. It follows that, whenever an institute accepts a fellow from one of the lesser developed countries, the situation to which he will return must be kept in mind. One must not neglect to put him on simple diagnostic isotope work of immediate practical value which he can continue in his own hospital and to teach him all aspects of isotope work including the principles of instrument repairs, etc. Only in this way will the training period be effectively utilized and the time and money spent on the fellow not wasted.

TRAINING COURSES

The organization of training courses in medical isotope applications is supplementary (or sometimes an alternative) to the fellowship programme. At the time of writing, a course is being conducted in Cairo, Egypt, and another will be organized in Athens, Greece, in spring 1962. A third is planned for 1963, in Buenos Aires, Argentina. The first two courses will last two months and twenty students, physicians and hospital physicists, have been accepted for each course. It is probable that the third course will be for ten students and will last four months. The lectures are given partly by teachers drawn from the host institute and partly by scientists from other countries (recruited by the Agency for this purpose) or by Agency staff members. The Agency also provides equipment for the course and pays for the travel and subsistence of the students. A syllabus has been drawn up which provides for about three weeks of basic training in physics, mathematics and chemistry, one week in radiation protection and waste disposal and three weeks for clinical applications. Therapy with radioisotopes is dealt with in the last week but external radiotherapy with Co-60 and Cs-137 is not included since it is felt that this subject should be dealt with in a separate course designed for radiotherapists and medical physicists. The mornings are reserved for lectures, the afternoons for practical experiments.

A great deal of thought has been given to the development of a standard syllabus for these courses but it must be admitted that the Agency is not entirely satisfied with it. It might be desirable to institute much longer courses, six months or perhaps a year, but financial limitations make this impossible. In any case, it is not believed that two months of even heavy indoctrination can provide sufficient training to enable the student to start medical isotope work on his own. No examination will therefore be held at the end of the course and no certificate of any sort will be handed out. It would be desirable to send the student on a one-year fellowship to an advanced laboratory to complete his training and it is hoped that at least some of the students now attending the course in Cairo will take advantage of this opportunity.

It should also be mentioned that the Agency often supplies lecturers for courses sponsored by other organizations; they come either from its own staff or are specially recruited from outside. This has been done for several courses conducted in South American countries during the last two years.

TECHNICAL ASSISTANCE

The second stage of the Agency's training programme is the dispatch of technical assistance experts to institutes and hospitals in the less advanced areas of the world. The expert spends six months or a year in the host country during which time he undertakes the setting up or expansion of medical isotope laboratories and initiates modest research projects of local interest, in co-operation with colleagues on the spot who have previously received training abroad. Frequently equipment is supplied with the expert to ensure that at least the basic tools for

his work are available. The first technical assistance project of the Agency involved the dispatch of an expert in nuclear medicine and other specialists in this field have been sent to Argentina, Austria, Ceylon, Greece, Guatemala, Iceland, Iraq, Israel, the Philippines, Thailand, the United Arab Republic and Yugoslavia; still others are being recruited for Brazil, Korea, Morocco, Paraguay, Tunisia and Turkey. So far, these experts have come from Austria, Czechoslovakia, France, Sweden, the United Kingdom and the United States. In general, hospital physicists are preferred to physicians, mainly because the required medical knowledge is usually available in the host country.

It must be admitted that it is rather difficult to find fully qualified candidates for the posts the Agency has to offer. First of all, there is a general shortage of personnel in all branches of nuclear science; secondly, the salaries paid are those of the United Nations and are frequently below those which physicists command in their own laboratories, particularly in the United States; thirdly, it is frequently difficult for a senior man to obtain prolonged leave of absence from his own institute; a further problem is that a highly specialized research man might in any case not be the best choice for the job. What is needed is an "all-round" man who can work completely on his own without auxiliary services, and can adapt himself to the working conditions in the host country. He must not only be able to teach all aspects of nuclear medicine—he is also expected to cope with such problems as finding the most economic method of ordering isotopes from abroad; persuading the local customs official not to tax a shipment of colloidal radiogold because it is bullion; getting the local mechanic to cast a lead collimator; or finding a method for the safe disposal of radioactive urine if the hospital sewerage system leads to an open ditch outside the hospital walls. Above all, he must have the type of personality which, under even the most difficult circumstances, creates a feeling of mutual trust between the expert and the local personnel. He must never allow any doubt to arise that his mission is to help them and their patients. The only real reward for his labours he is likely to find is the feeling that he has accomplished something really worthwhile, that he has contributed—if only a trifle—towards combatting the misery of the helpless. If he is lucky he might also find a research problem of more than local interest, the study of which will satisfy his investigative mind; there might be diseases he has never heard of and to which modern research techniques have so far not been applied. Much could be gained if it were possible to extend these technical assignments over several years but, unfortunately, the Agency's financial resources do not permit this—and recruitment would be even more difficult than it is already.

THE RESEARCH CONTRACT PROGRAMME

This is the third step in the Agency's technical assistance activities. Contracts are awarded to institutes whose staff is in a position to carry on research without outside advice. Under the terms of a contract the Agency pays the salaries of additional postgraduates and technicians, defrays the costs of expendable

supplies required for the work and puts at the disposal of the institute the necessary additional equipment. The majority of the medical research contracts have gone to institutes in tropical areas and are designed to support research on diseases which affect a large part of the population. At present, medical research of this type is supported in Greece, India, Iraq, Israel, Kenya, the Philippines, South Africa, Thailand and Venezuela; the subjects are, inter alia, radioiodine metabolism in endemic goitre, iron metabolism and red cell life span in hereditary haemolytic anaemias, protein metabolism in malnourished individuals and scintigraphic localization of echinococcus cysts in the liver. It will be immediately obvious from this list that these contracts do not support research in the original meaning but rather that they are designed to assist in applying known techniques to problems peculiar to the tropics. Since the Agency has no expert on tropical medicine on its own staff, it relies on the specialists in parasitology and entomology and in nutritional and endemic diseases of the World Health Organization. It is hoped that this collaboration will become even closer in the future.

The Agency has other medical research contracts which support research in its narrower interpretation. An example of this kind is the group of about a dozen contracts which have been awarded to institutes working with the isotope calcium-47. Naturally, most of these are placed in the more advanced countries and the Agency in fact only covers the costs of the isotope itself since these institutes can be expected to pay for salaries and equipment from their own resources. It took the Agency nearly two years of work—including market surveys and expert meetings—to convince commercial producers that it would be worthwhile for them to start production of this isotope and it is pleasing to note that calcium-47 is now freely available on the market, that its contamination with calcium-45 is reasonably low and that its price has dropped from $1400 per millicurie in 1958 to $200 per millicurie at present. Most of the work with this isotope concerns the absorption and accretion into bone of calcium under normal and pathological conditions such as osteoporosis, vitamin-D deficiency, Paget's disease, etc., whereas other institutes are using Ca-47 mainly for the detection and localization of bone tumours. The Agency not only supports this work by paying for the isotope but also assumes a co-ordinating role. In December 1961, a meeting in Vienna brought together all principal investigators and a few other leading groups to discuss the progress so far made, to compare the results and to decide the direction in which further efforts should be made.

CONFERENCES AND SYMPOSIA

Of the conferences and symposia organized by the Agency every year, at least one has so far always been devoted to a medical subject. In 1959, there was a symposium in Vienna on Medical Radioisotope Scanning (4),—this indeed was the first scientific meeting which the Agency ever arranged—, and in 1960 one in Bangkok on the Use of Isotopes in Tropical Medicine (5); both meetings were jointly organized with the World Health Organization. In 1961 a symposium on Whole Body Counting was held in Vienna (6) and a conference on the Use

of Isotopes in Animal Biology and the Medical Sciences in Mexico City (7).

It will be observed that these meetings are usually centred around a tool, namely radioisotopes, or a particular technique such as scanning. That approach has so far proved to be quite successful but many people might wonder whether one should not choose a medical problem as the central subject and discuss its possible solution by means of various tools, only one of which would be isotopes. Valuable as this approach may be, the Agency is primarily concerned with atomic energy as a tool and it is felt that meetings of the second type should be left to the medical societies or organizations. In any case, much can be said in favour of *small* meetings with not more than, say, 50 or 60 participants in which a limited number of papers on a limited subject are arranged in such a way that there is at least as much time for discussion as for the presentation of the papers themselves. It has been the Agency's experience that a great deal of valuable information emerges only if sufficient time is allowed for lively discussion between the speaker and the audience. Occasionally, however, the Agency is called upon to organize a large conference on a broader subject and here the aim is to bring together scientists working in different fields but using the same or closely related techniques. An example was the conference on the Use of Radioisotopes in Animal Biology and the Medical Sciences in Mexico City. In order to avoid the rush of "10-minute paper and 3-minute discussion", the Agency suggested to the authors that their papers could be as long as they wished but that, since the full text would be available in pre-printed form, they would have only 5-10 minutes for presenting the highlights, followed by 15 to 20 minutes for discussion.

PROBLEMS OF COBALT-60 TELETHERAPY

The preparation of training courses, scientific meetings and technical assistance projects occupies a great deal of the time of the staff of the Medical Section, although the bulk of the administrative work connected with these programmes is, of course, borne by other Divisions of the Secretariat (such as the Division of Exchange and Training, or the Division of Economic and Technical Assistance) and the Medical Section's contribution is essentially of an advisory nature. Of the other numerous activities of the staff which, for lack of a better description, are called studies, only two projects which have been under way for some time will be described.

The first is concerned with the use of high-energy radiation for radiotherapy and in particular with cobalt-60 teletherapy units. These units offer considerable physical and economic advantages and it is not surprising that their use has increased rapidly in the past 10 years. At present there are at least one thousand such installations in operation in different parts of the world. To assist those planning radiotherapy facilities, the Agency published in 1959 an "International Directory of Teletherapy Equipment" (8) and this is kept up to date as new technical and other information on teletherapy equipment and sources is collected. A complementary publication, which has also proved widely useful, is the "Bibliography on the Application of High Energy Radiation in Therapy" (9).

The main problem in cobalt-60 teletherapy is not however the choice of equipment but its proper utilization once installed. It must be admitted that many—perhaps the majority—of the existing units are located in institutes which are short of trained staff and have little or no auxiliary measuring equipment. As a result, the cobalt unit cannot be employed effectively since the radiation output is not known accurately and the distribution of dose in the various individual circumstances of treatment is not properly assessed. The Agency is tackling this problem in three ways: by furthering the training of physicians and physicists in radiotherapy, by providing as much physical data as possible from outside sources (thus reducing the amount of measurement or calculation needed locally) and, where necessary, by providing assistance in installing teletherapy units and in carrying out basic physical measurements. The latter type of assistance has been provided to China, Greece, Iran, the Philippines and Thailand. Early in 1959 the Agency made a world-wide survey of the use of large radiation sources in radiotherapy. The results of this survey were considered, in August of the same year, by an international study group which was convened jointly by the World Health Organization and the Agency. The recommendations of the group were published in 1960 (10) and cover various aspects of teletherapy—technical, economic, staffing and training. These recommendations have been translated into seven languages and have received very wide attention. There will be another panel meeting in 1962, specifically to discuss the problems of operating radioisotope teletherapy units in less advanced countries. Another method of utilizing and further training existing staff is through active co-operation, on a regional basis, of several radiotherapy centres. Plans are being prepared for such co-operation, first in the Middle East, later in other parts of the world.

The collection and distribution of physical data for radiotherapy is an enormous task, but is being undertaken systematically on a long-term basis. Early in 1960 the Agency carried out a survey of existing dose distribution data for high-energy radiation. This survey was undertaken in co-operation with several national organizations of hospital physicists. In November 1960 a panel meeting on Physical Data for Dose Distribution with High-Energy Radiation was convened in Vienna. Following the recommendations of this panel (11), the Agency is gradually establishing an "international clearing house" for the provision of physical data on radiation dose distributions. Several publications are now in preparation, including an international catalogue of single-field isodose charts (12) and atlases of representative dose distributions of single, multiple and moving beams (13). These atlases are intended for both teaching and reference purposes. As a preliminary to these collections of data for high-energy radiation, an atlas of single-field isodose charts for 250 kV X-rays was found to be necessary and has been published (14). A second panel meeting, on Standardization of Radiological Dosimetry for Radiation Beams, was convened jointly by the Agency, WHO and ICRU in April 1961. The recommendations of this panel are to be published later, through ICRU. The measurement of the output of cobalt units has received special attention, a small group of experts being convened in Vienna in December 1961 to discuss possible methods of standardization.

THYROID UPTAKE STUDIES

The other project which will be described briefly is the international calibration and standardization of thyroid radioiodine uptake measurements. This is still the most widely practised medical application of radioisotopes but there are hardly two laboratories in the world which use precisely the same technique. A certain amount of standardization would undoubtedly help greatly to achieve satisfactory comparability of results obtained in different parts of the world. Dr. Marshall Brucer's mannequins filled with so-called "mock iodine" which he sent round to laboratories in the United States and England, are still very much remembered. The Agency's project also provides for the use of such a mannequin but it is hoped, of an improved design. The first object of sending this girl out on the road is to allow participating laboratories to see how accurate their own technique is, and to calculate, if necessary, appropriate correction factors. However, the Agency had to go one step further than the Oak Ridge group in that a standard method of uptake measurement had to be developed which would be acceptable to all and which could be adopted by those whose present method is clearly unsatisfactory. Late in 1960 the Agency convened a small group of leading experts to discuss such a standard method, and it was indeed possible to reach agreement on a set of recommendations which are being published (15). It was also found that much would be gained if an Agency expert could be sent along with the equipment to Member States requesting such service, so that he could not only supervise the calibration of the existing equipment but also train staff of the laboratory. They in turn could calibrate equipment in other laboratories in the same country. This procedure will be followed, and the expert set out on his first tour in February 1962.

THE AGENCY'S LABORATORIES

The Agency's two laboratories, of which one is situated in Seibersdorf near Vienna, adjacent to the Austrian reactor centre, and the other in the Headquarters building, have a number of well defined tasks. There is, for example, a section which prepares precise standards of the more commonly used isotopes; there is an environmental contamination section which measures fall-out contamination of samples from Member States not having facilities of their own; there is another section in which the tritium content of ocean, river and rain water samples from all over the world is determined, and so on. Officially, however, there is no provision for medical research and, therefore, there is no money. Nevertheless, thanks to a generous research grant by the U.S. Atomic Energy Commission, the Agency is at present setting up a whole-body counter with an iron room, an 8-inch crystal, a 400-channel analyser and all that goes with it. Work started in March 1962. During the first year much time will be devoted to measurements on some 100 human subjects living in or near Vienna who were given the colloidal radioactive compound Thorotrast for diagnostic radiology some twenty years ago. This will be part of a somewhat larger project to study the effects of contamination of human subjects with various radioactive substances. The Agency is already supporting whole-body measurements of strontium-90 burdens in dial

painters in Czechoslovakia and Poland and of Laplanders in Scandinavia who carry substantial amounts of fission products due to their particular feeding habits. However, it is also planned to do metabolic experiments with intentionally administered isotopes and it is hoped that the planned collaboration with the Vienna University hospitals will be particularly fruitful in this respect.

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Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

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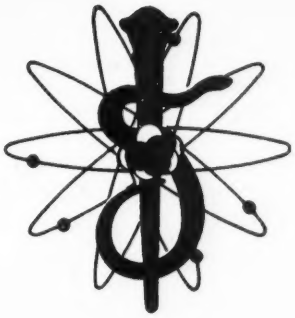

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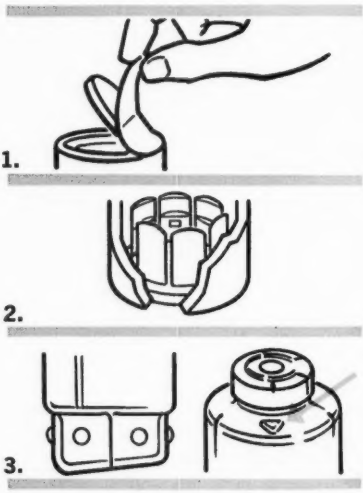

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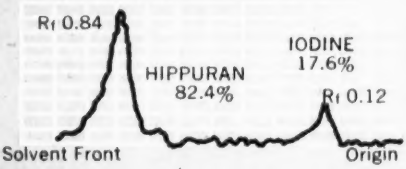

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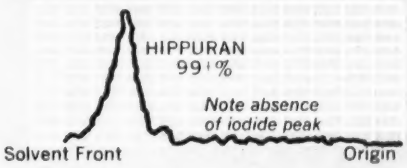

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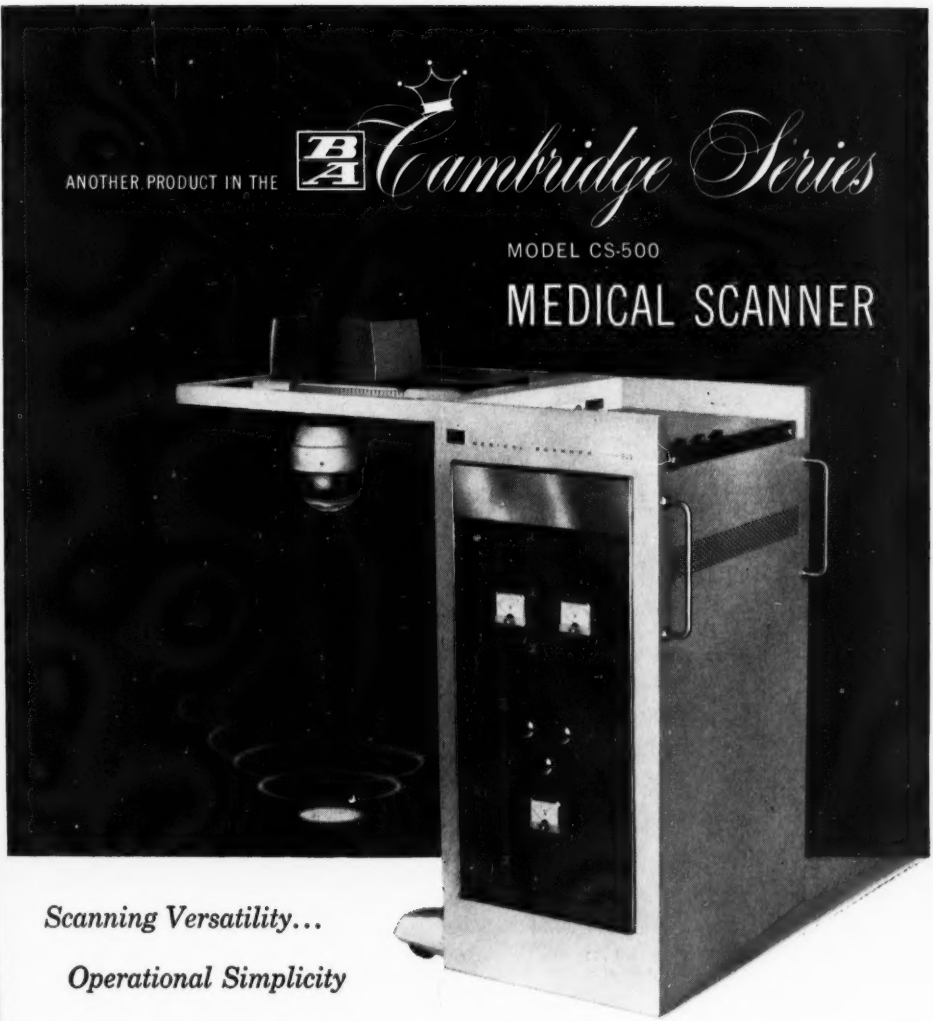

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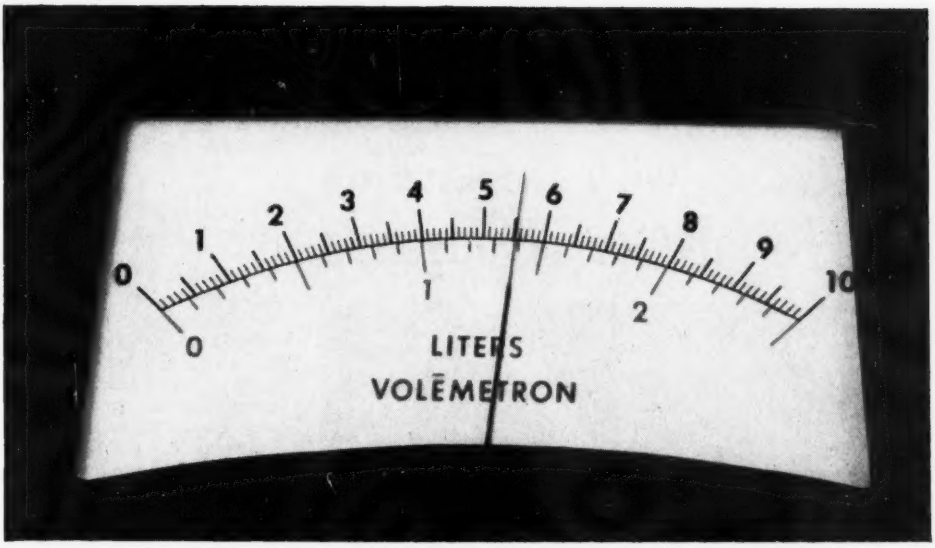

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Versatile instrument systems for renal function studies with radioiodine labelled compounds

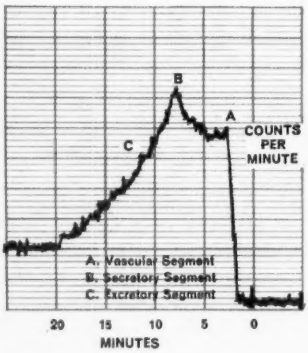
The radioisotope renogram presents a graphic record of individual kidney function. Information is obtained rapidly by means of a simple external procedure. Its reliability in establishing the presence or absence of renal dysfunction has made the renogram a rapidly adopted, valuable method of screening patients prior to extensive urologic examinations.

Nuclear-Chicago's renal function systems are designed to serve the diverse needs of physicians. Since future plans, budget, and adopted procedure play an important role in the choice of a renal function system, a variety of systems should be considered before selection.

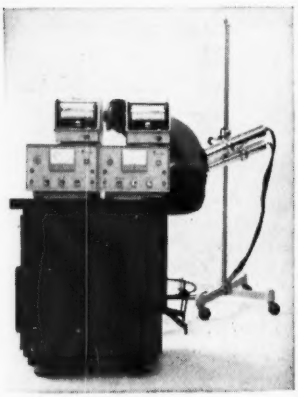
Nuclear-Chicago produced the first renal function system in 1955 and alone offers the physician almost a dozen different systems to choose from. A few are illustrated and described in the columns to the right. They represent only a small portion of Nuclear-Chicago's instrument systems for nuclear medicine. Please ask us to send you additional information.

Basic renal function system

This system was developed over seven years ago and is now used in more hospitals than any other renal function system. Low-cost and compact, it has become the standard system for renal function studies in smaller clinics, hospitals, and medical centers. The system requires a working space of only three feet square by six feet high. It can easily be moved from room to room. Associated readout instrumentation can be placed on a nearby desk or table. The probes are easy to position for either a seated or reclining patient. Chart recordings of each kidney are simultaneously produced as the probes follow the appearance and clearance of radioactivity.



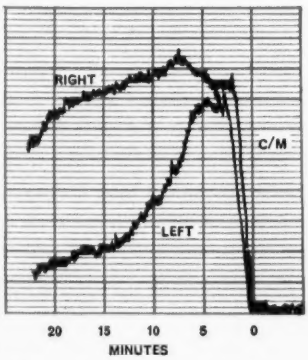
Recording of normal kidney function obtained from one recorder in the system.



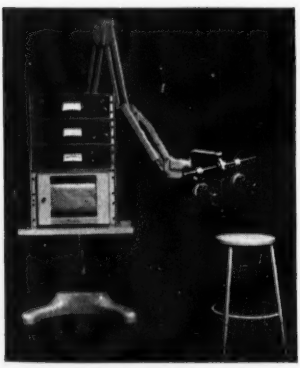
The basic system consists of the SA1 stand with two arms, dual DS101 one-inch crystal probes, dual 1620CS rate-meters and dual R1000A chart recorders.

Single-arm renal function system

The single-arm design of the 4125 system below permits quick, easy positioning of two or three scintillation probes. The probes are mounted in a unique "T" clamp. Two can be positioned for kidney readings. A third probe can be used if desired for following the clearance of activity from the circulatory blood. The counting and recording instruments are mounted on the stand's shelf. The recorder features dual pens which produce superimposed recordings of the function of each kidney in different ink colors. A third recording is made simultaneously in the three-probe modification of this system.



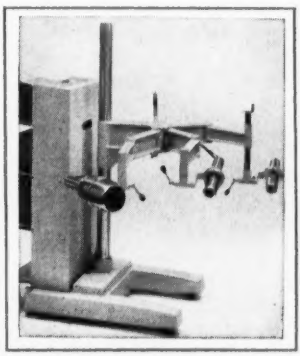
Typical recording obtained with the dual-pen recorder. Note ureteral obstruction of the right kidney.



The 4125 single-arm system consists of the SA2 stand, 1725 probe clamp, dual DS101 one-inch crystal probes, two 6350 Logic ratemeters, an 8200 high voltage supply and an 8411 dual-pen recorder.

Complete clinical system

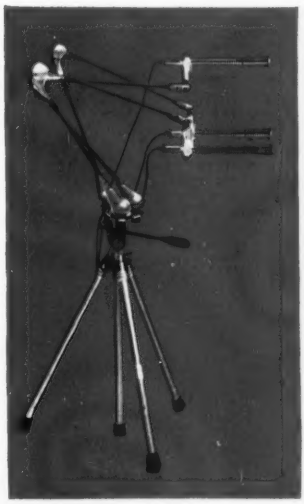
Recent papers on renal function studies have suggested the use of three and sometimes four scintillation probes. Some papers have also suggested the use of heavily collimated two- and three-inch crystal scintillation probes. The 1710 is the only clinical stand available which accommodates these diverse requirements. It can be used with one-, two-, or three-inch crystal scintillation probes. Its three arms equipped with special "T" clamps can support as many as six scintillation probes. A precision motor drive with finger-tip control permits easy vertical positioning of the probes at any height with respect to the patient. Ample space in the instrument rack is provided for holding renal function instruments as well as instruments for other in-vivo procedures.



The 1710 clinical stand can be supplied with one, two, or three arms and with or without the instrument rack. This versatility makes it particularly interesting to the hospital or medical center that expects to expand its isotope facility at some future date. Each of the three arms can safely support 80 pounds. This permits a shielded 3-inch crystal detector or two shielded 2-inch crystal detectors to be mounted on a single arm.

Iodine-125 clinical system

Iodine-125 has recently been studied in renal function tests and in other diagnostic applications of radioisotopes. The advantages of I-125 over iodine-131 are longer half life and thus longer shelf life, lower radiation exposure to the patient, and the ability to use lighter weight and less expensive scintillation detectors. The latter advantage is possible because of the low energy of the principal photon radiation (27.3 kev). This low energy permits reduction of crystal and collimator size producing a considerable decrease in background.



Nuclear-Chicago's I-125 system consists of the 1783 three-arm stand equipped with two or three Model 645 I-125 probes with special brass collimators. The third scintillation probe is used to record the clearance of the labelled compound from the blood stream. It is usually positioned at the posterior thorax. The Model 645 I-125 scintillation probe has a 2 mm thick by ¼-inch diameter sodium iodide crystal, a specially selected, low-noise, high-gain photo-multiplier tube and a special brass, flat-field collimator.

NUC:D-2-269

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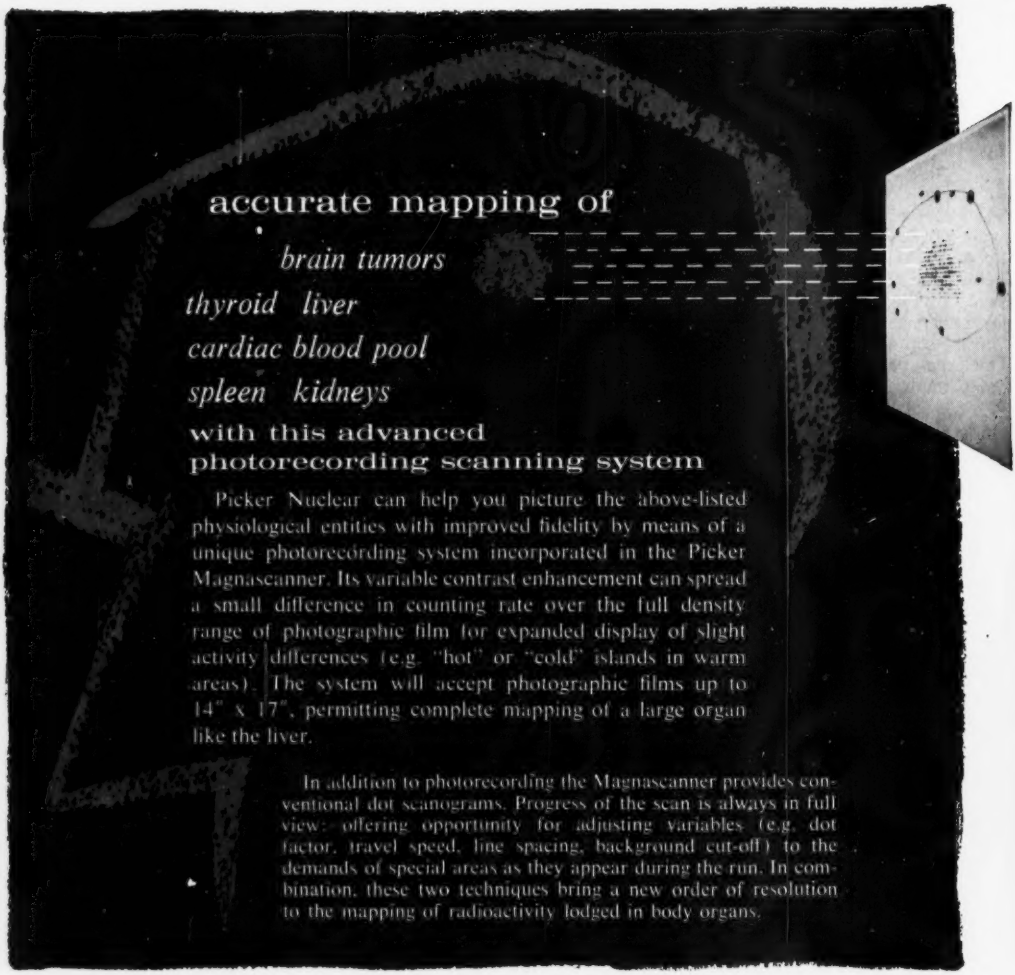
accurate mapping of
brain tumors
thyroid liver
cardiac blood pool
spleen kidneys
with this advanced
photorecording scanning system
Picker Nuclear can help you picture the above-listed physiological entities with improved fidelity by means of a unique photorecording system incorporated in the Picker Magnascanner. Its variable contrast enhancement can spread a small difference in counting rate over the full density range of photographic film for expanded display of slight activity differences (e.g. "hot" or "cold" islands in warm areas). The system will accept photographic films up to 14" x 17", permitting complete mapping of a large organ like the liver.
In addition to photorecording the Magnascanner provides conventional dot scanograms. Progress of the scan is always in full view: offering opportunity for adjusting variables (e.g. dot factor, travel speed, line spacing, background cut-off) to the demands of special areas as they appear during the run. In combination, these two techniques bring a new order of resolution to the mapping of radioactivity lodged in body organs.

The Magnascanner is one of the comprehensive Picker line of nuclear instrumentation and supplies: all marketed and serviced through a national network of company offices staffed by trained Picker people. (Picker alone in the nuclear field offers this caliber of local service).

For details call your district office (see 'phone book) or write Picker X-Ray Corporation, 25 South Broadway, White Plains, New York.

Picker nuclear

Here's the Picker Magnascanner being readied for a thyroid scan. The heavily shielded probe and companion precision instrumentation are mounted on a freely maneuverable mobile carriage.

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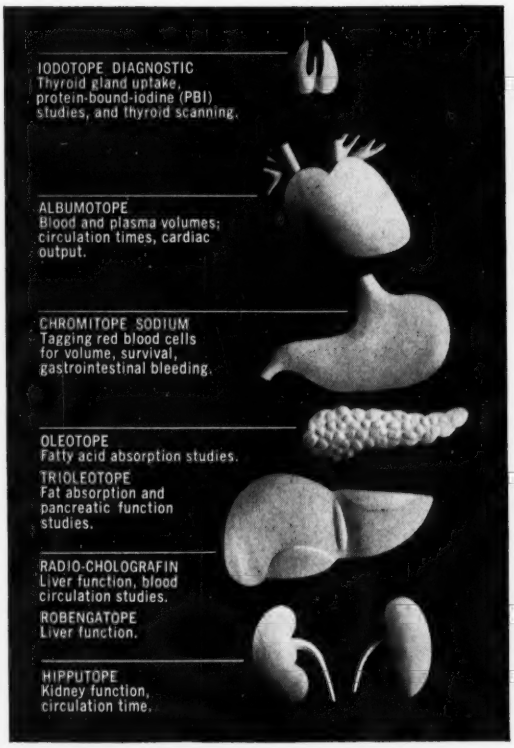

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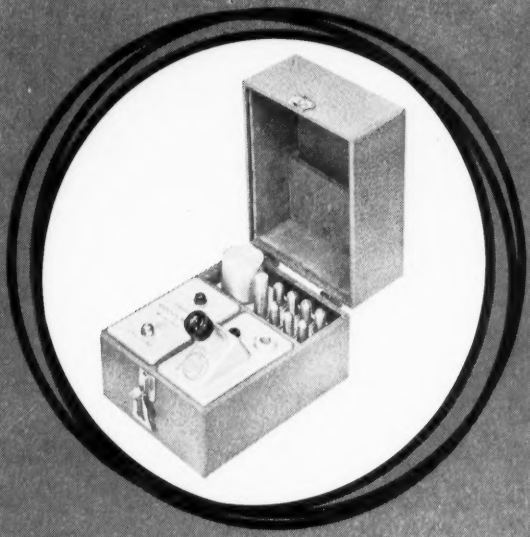

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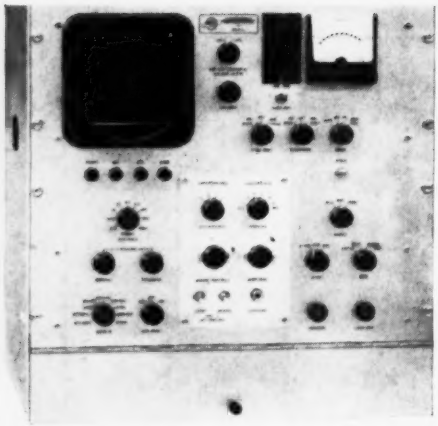

RIDL Model 34-12 Analyzer

with RIDL MODEL 34-12

400-CHANNEL PULSE HEIGHT ANALYZE

used with...

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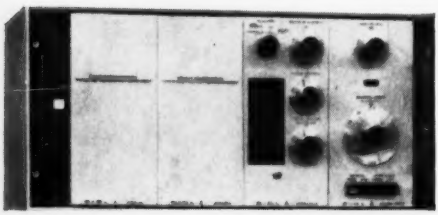
DESIGNER SERIES

ANALYZER ACCESSORY SYSTEMS

MODEL 88-901 TIMER SYSTEM provides time base and gating action to expand the control capabilities of the Analyzer and to extend Automatic Time Mode Operation for the experiments listed above.



The Model 88-901 Timer System is a DESIGNER SER instrument. The two plug-in instruments are contai within the Model 29-1, a four unit instrument case power supply.

BASIC TIMER, MODEL 54-6 Provides: • Time b channel advance pulses and gated channel widths w crystal controlled accuracy • Active counting intervals channel of 12.5 microseconds to 800 seconds. • Manual external start pulse to synchronize with pulsed exp ments • Automatic stop at end of selected cycle*

TIME MODE CONTROLLER, MODEL 52-9 Provid •Preset Counter to count 1 to 900 cycles, in 27 steps • In ates the read process (print, record etc.) of the analy • Visual readout of completed cycles • Cycle consists complete address scan of a selected memory group

0.1 microseconds pulse pair resolution.

HIGH SPEED SCALER KIT MODEL 52-36 —Replaces one standard data scaler board in the RIDL Model 34-12 Analyzer to increase pulse pair resolution to 0.1 microseconds.

*The Basic Timer, Model 54-6, may be operated without Model 52-9 Time Mode Controller.

SEE RIDL ANALYZER SYSTEMS AND DESIGNER SERIES INSTRUMENTS AT THE ATOM FAIR—BOOTH 140-141

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